Exploring cardiotoxic effects of post-myocardial infarction depression

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Dissertation

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rijksuniversiteit groningen

Stellingen behorende bij het proefschrift

Exploring cardiotoxic effects of post-myocardial infarction depression

Marij Zuidersma

In observationeel onderzoek is depressie na een hartinfarct geassocieerd met een slechte hartprognose, maar het experimenteel manipuleren van de depressie in studies met een gerandomiseerde opzet leidt niet tot verbeteringen in de hartprognose. Hieruit kan geconcludeerd worden dat depressie na een hartinfarct geen causale risicofactor is voor de slechte hartprognose *(dit proefschrift)*.

Traditionele depressiebehandelingen bij hartinfarctpatiënten leiden niet tot verbeteringen in de hartprognose, omdat zij niet zijn gericht op het veranderen van de mechanismen die ten grondslag liggen aan het verband tussen depressie en hartprognose, zoals de conditie van het hart zelf *(dit proefschrift)*.

Traditionele depressiebehandelingen bij hartinfarctpatiënten leiden niet tot verbeteringen in de hartprognose, omdat ze nauwelijks tot verbeteringen in de depressie zelf leiden *(dit proefschrift)*.

Om een zo goed mogelijke inschatting te maken van de hartprognose van een hartinfarctpatiënt, kan men de patiënt beter een depressievragenlijst laten invullen dan een diagnostisch interview voor depressie afnemen *(dit proefschrift)*.

Hartinfarctpatiënten die ervoor kiezen om hun depressie te laten behandelen hebben een betere overlevingskans dan diegenen die daar niet voor kiezen, maar dit komt niet door de depressiebehandeling zelf *(dit proefschrift)*.

Zolang er geen effectievere depressiebehandelingen voorhanden zijn, zullen de voordelen van het structureel testen op depressie bij hartinfarctpatiënten niet tegen de nadelen opwegen *(dit proefschrift)*.

Doordat studies naar depressiebehandeling alleen zijn uitgevoerd onder hartinfarctpatiënten die voldoen aan criteria voor de diagnose depressie, waren de inclusiecriteria niet optimaal om de effecten van depressiebehandeling op hartprognose te evalueren *(dit proefschrift)*.

Het doen van onderzoek is te vergelijken met het uitvoeren van een muziekstuk. Je moet op de details letten, maar het geheel is waar het om gaat.

cmb.

RIJKSUNIVERSITEIT GRONINGEN

Exploring cardiotoxic effects of post-myocardial infarction depression

Proefschrift

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INTRODUCTION

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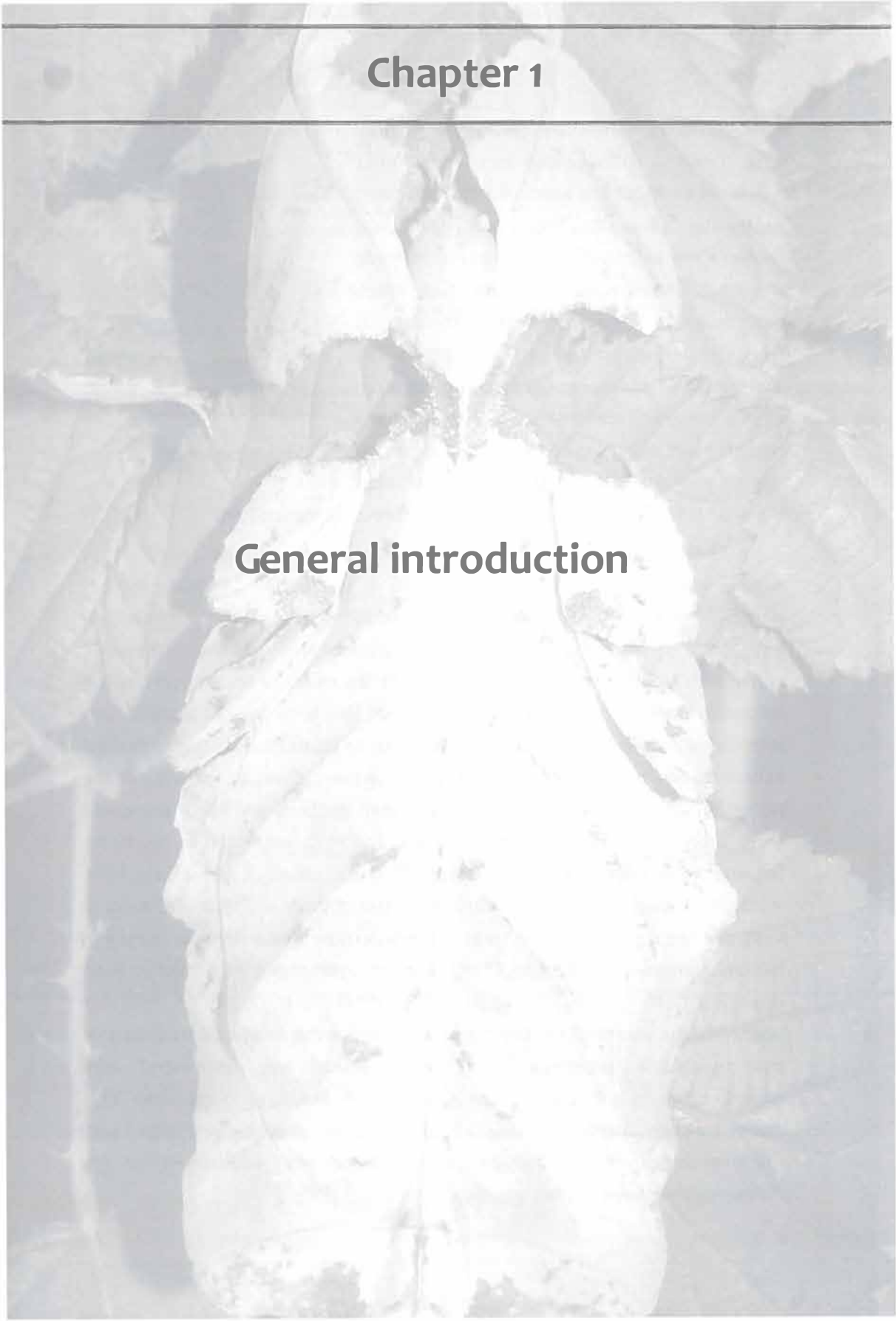

General introduction

Hoagy Carmichael

In 1938 Hoagy Carmichael wrote the popular song 'Heart and Soul'. Like him, many other artists wrote about the heart and the soul being intertwined. The title 'Heart and Soul' was chosen for at least twelve songs and eight music albums. Several movies, books and poems share this title and numerous others share the subject. Thus, the connection between the heart and the soul has been widely recognized. The breaking-up of a romantic relationship is said to result in a broken heart. Listening to your heart means to rely on your feelings. But the relation between the heart and the soul seems to go further than feelings and love.

That diseases of the heart and diseases of the soul go together has already been argued centuries ago. In 1628, the English physician William Harvey, who discovered that circulation of the blood was due to the mechanical function of the heart, said that "every affection of the mind that is attended either with pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart" (1). In 1818, the term 'psychosomatic' was introduced by the German physician Heinroth to illustrate that close relations exist between the body and the soul (2). However, it was at the start of the twentieth century that the integration between the body and the soul became more accepted in medicine. Between 1918 and 1932, education in psychiatry became a fundamental part of general medical education (3). At the same time, scientific interest in the interrelationship between body and soul increased. In 1935, the term 'psychosomatic' was re-introduced by Helen Flanders Dunbar in her book Emo*tions and* Bo*dily Changes* (4). In 1936, Wolfe identified in heart disease patients how psychological factors, in particular anxiety neurosis, can aggravate the course of the heart disease and how the successful treatment of the psychiatric problems with psychoanalysis was associated with improvements in the heart disease (5, 6). In 1937, Malzberg found death rates due to diseases of the heart almost 8 times higher in patients hospitalized with mood problems than in the general population after adjustment for age differences between the two groups (7).

What is a heart attack?

A heart attack (myocardial infarction (MI)) follows after the occlusion of a coronary artery. The coronary arteries provide the heart muscle with blood. Occlusion of a coronary artery therefore leads to a blockage in the blood-flow supplying oxygen to the heart muscle resulting in death of the tissue of the heart muscle. Mostly, the injury to the heart muscle presents itself with chest pain. Too much injury of the heart tissue results in a worsened pump function of the heart. The left ventricular ejection fraction is a measure of the function of the left ventricle and is a strong predictor of recurrent cardiac events and mortality.

Pathway to the development of a heart attack

A major pathway preceding MI is atherosclerosis, which is the formation of a plaque on the artery-wall. During the life-course, lipids and white blood cells stick on small fractures on the inner side of the artery-wall, creating a plaque. This process is named atherosclerosis and results in the narrowing of the artery and makes the artery stiff. It is not the narrowing of the vessel due to the plaque itself that precipitates MI. However, disruption of the upper layer (fibrous cap) of the plaque stimulates thrombosis: the creation of a blood clot on the location of the plaque, which can occlude the artery partly or completely (8).

Diagnostic criteria for MI

According to the criteria of the World Health Organization (WHO) a patient is diagnosed with MI when at least two of the following criteria are met: 1) chest pain for at least 20 minutes, 2) typical changes in the electrocardiogram (ECG), and 3) a typical rise and fall of cardiac enzyme levels (9).

Prevalence and epidemiology

In 2008, 14 out of 10.000 people in the Netherlands were admitted to a hospital for MI. This rate was twice as high for men than for women and increased with age (see **Figure 1**). Eight percent of women versus 6% of men died during hospitalization for MI in 2008 (10). Of those who survive hospitalization for a first MI, 44% will be readmitted to the hospital for cardiovascular disease within the following 5 years, of whom half during the first 7 months (11).

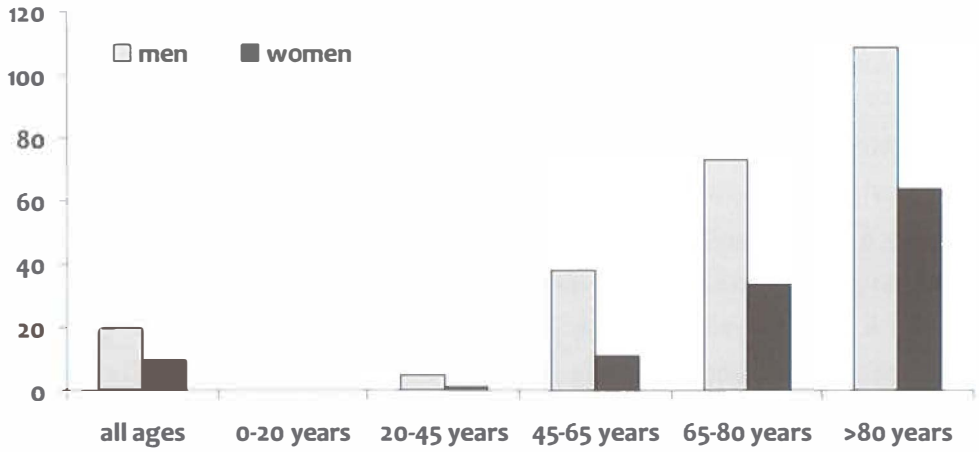

Figure 1. Number of hospital admissions per 10,000 persons in the Netherlands in 2009 for heart attack by age (source: CBS)

Between 1970 and 2000, mortality due to MI has decreased substantially in developed European countries, including the Netherlands (12, 13). This decrease is attributed to changes in diet, lifestyle factors and improvements in modern cardiovascular treatment (13). However, the decreased mortality rates run parallel with increasing numbers of patients with chronic heart disease (14). This increasing number of patients with chronic heart disease emphasizes the need to manage the disease and control risk factors for its development and progression.

Treatment

In-hospital treatment of MI is aimed to rapidly restore the coronary blood flow, which is called reperfusion. It is of utmost importance that the blood-flow is restored as fast as possible to minimize the necrosis of myocardial tissue. Therefore, treatment can already start before reaching the hospital. There are two ways of reperfusion: pharmacological reperfusion and mechanical reperfusion. Pharmacological reperfusion is the rapid restoration of coronary blood flow by means of pharmacological treatment. Thrombolytic therapy is the administration of a drug that dissolves blood clots. Antiplatelet treatment is drug treatment with for example aspirin to reduce aggregation of blood platelets. Other drugs inhibit thrombin, a protein involved in the blood-coagulation. Mechanical reperfusion is the restoration of coronary blood flow by percutaneous coronary intervention (PCI). One example of PCI is angioplasty. With angioplasty, a balloon placed on a catheter is entered into the coronary vessel. At the narrowed place the balloon is inflated, thereby opening up the blockage. Then the balloon is deflated and removed. Instead of the balloon, a stent can be inserted: a tube that stays behind in the coronary artery to keep it open (see **Figure 2**). After discharge, several drugs are temporarily and permanently (i.e. for the rest of a life-time) prescribed that decrease the risk of recurrent cardiac events.

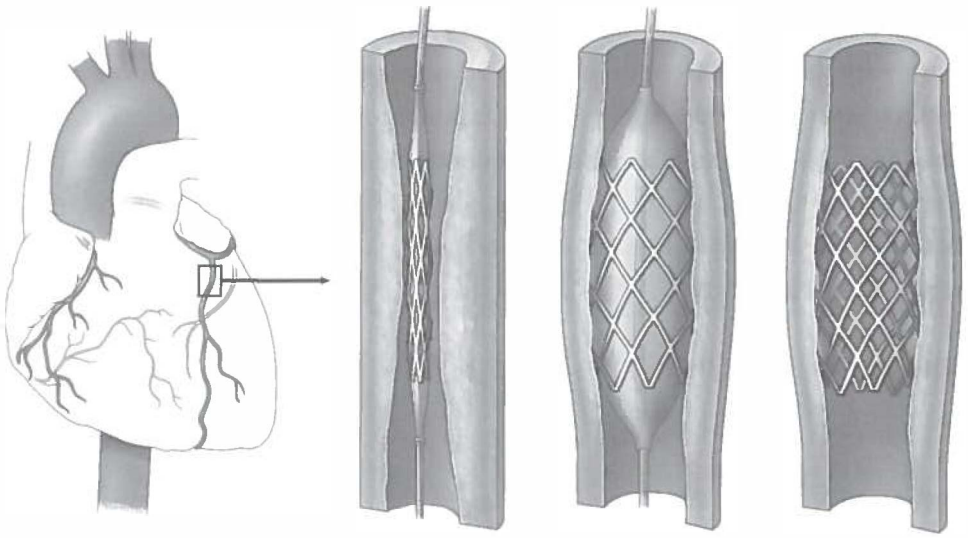

Figure 2. Insertion of a stent into a coronary artery

Factors associated with the clinical course and outcomes of the heart disease

The risk of development and progression of heart disease increases with age and is higher in men than in women. On average, women are 10 years older when heart disease manifests itself (15).

Biological factors associated with heart disease are lipid levels, inflammation and blood pressure. Lipids circulating in the blood, among which cholesterol, are involved in the development of the plaque and are associated with heart disease (16). Reduction in cholesterol-levels is associated with reductions in the development and improvements in the clinical course of heart disease (17). Inflammation plays an important role in plaque disruption. Circulating levels of inflammatory markers such as C-reactive protein and interleukin-6 are associated with the development, clinical course and outcome of the heart disease (18, 19). High blood pressure demands the heart to work harder and damages the blood vessels and is also associated with the development and clinical course of heart disease (20). One important risk factor for heart disease is diabetes mellitus. Individuals with diabetes mellitus have a two-fold increased risk of developing heart disease compared to non-diabetics (21).

Lifestyle and behavioral factors, such as diet and body weight, smoking, and physical activity influence these biological risk factors and, in turn, predict the development and clinical course of heart disease. Modification of these factors strongly reduce the risk and progression of heart disease (22, 23). Therefore, cardiovascular disease prevention is targeted to modify lifestyle (15). Factors that affect lifestyle changes are low socio-economic status, low education, living alone, stress at work or home, and negative emotions, among which depression (15).

What is depression?

Depression is a mood state during which a cluster of psychological and physical symptoms is present for a certain period. It includes emotional (e.g. depressed mood), motivational (e.g. loss of interest or pleasure), cognitive (e.g. negative thoughts, feelings of hopelessness), and somatic (e.g. loss of energy, sleep disturbances) symptoms (24, 25). Most people experience some of these symptoms from time to time. However, when they become too intense, causing significant distress and disability to engage in daily activities, social life and work, the depression is described as a clinical depression in need of treatment.

Pathways to the development of depression

Predictors of depression seem to differ between patients and it is never certain whether a specific factor was the actual cause of the depression. In addition, depression appears to be caused by an interaction between multiple factors. Stressful life events, such as job loss or divorce play an important role in the onset of depression (26-28). Still, most individuals who experience a stressful life event will not get depressed. Several psychological and biological factors seem to make some individuals more vulnerable than others to develop depression after a stressful life event.

Psychological factors affecting vulnerability to stressful life events

One psychological factor that makes individuals more vulnerable to develop depression after a stressful life event is neuroticism, which is described as a tendency to experience negative emotional states (28, 29). Also individuals who have to cope with chronic stressors, such as a chronically ill spouse or poverty, are more vulnerable to develop depression after a stressful life event (29). Another factor that makes individuals vulnerable to stressful life events is cognitive inflexibility. Individuals who automatically blame themselves or others for the problem, imagine the problem is unsolvable and that it will affect all areas of their life are more vulnerable to develop depression after a stressful life event than individuals who do not automatically blame themselves or others for

the problem, think of it as temporarily and solvable and find it affecting only limited areas of their life (30, 31). A passive coping strategy (i.e. avoidance) may make individuals more vulnerable to depression after a stressful life event than an active coping strategy (i.e. seeking social support, engaging in activities) (31). Reduced social support may make individuals more vulnerable to depression after a stressful life event by constraining coping resources and increasing loneliness (31).

Biological factors affecting vulnerability to stressful life events

One important biological factor suggested to play a role in the pathway to depression is a deficiency and/or a diminished action of serotonin and noradrenalin (i.e. the mono-amine hypothese), on which the action of some types of antidepressant medications are based (32). Furthermore, individuals with the short allele of a gene involved in the action of serotonin have been found to be more vulnerable to develop depression in the presence of a stressor than individuals with the long allele of that gene (33). Another potential pathway to depression is the increased production of the hormone cortisol due to stress. Depressed and non-depressed individuals seem to have similar cortisol levels just before and during a psychological stressor, but the decrease in cortisol levels after the stress is ended is larger in non-depressed individuals (34). This suggests that some individuals are more vulnerable to stressors increasing their risk for depression. Some studies suggest that depression is associated with reduced neurogenesis in the brain and reduced levels of growth factors involved in the neurogenesis (32). Recently it has been suggested that a pro-inflammatory state may be a pathway to depression (35). A pro-inflammatory state as a reaction to an infection, like the flu, is often associated with feelings of decreased appetite, diminished interest in engaging in activities, fragmented sleep, and difficulties to concentrate. Depressed patients have been found to have increased levels of inflammatory markers such as C-reactive protein and interleukin-6 compared to non-depressed individuals (36).

Establishing a diagnosis of depression

Because of its subjective nature and lack of consistent evidence for biological markers, it is much more difficult to establish a diagnosis of depression than a diagnosis of a physical disease, like MI. Instead of a laboratory test or medical examination, the diagnosis of depression is made with a diagnostic interview. During a diagnostic interview the patient is asked for the presence of depressive symptoms and their interference with daily activities, social life and work. Examples of diagnostic interviews are the Composite International Diagnostic Inverview (37) and the Diagnostic Interview Schedule (38). There are two systems that construct the criteria for diagnosing psychiatric disorders: the Diagnostic and Statistical Manual of Mental Disorders (DSM) (24) and the International Classification of Diseases (ICD) (25). The Box shows the diagnostic criteria for a major depressive episode according to the DSM fourth edition (24).

Questionnaires to screen for the presence of depression

A questionnaire may be used as a rapid screen for the presence of a depressive episode. Instead of yielding a diagnosis of major depression, a questionnaire assesses the current presence and severity of depressive symptoms. Several questionnaires exist, evaluating different sets of symptoms. Some, like the Center for Epidemiologic Studies Depression Scale (39), include mainly cognitive and affective symptoms of depression (low mood, feelings of guilt and worthlessness, low self-esteem, hopelessness and demoralization). Other questionnaires, like the Beck Depression Inventory (40), include also somatic symptoms of depression (for instance decreased energy levels, irritability, sleeping problems, appetite problems and weight change).

BOX: DIAGNOSTIC CRITERIA FOR A MAJOR DEPRESSIVE EPISODE ACCORDING TO THE DSM (FOURTH REVISION) (24).

Symptoms of depression

(1) depressed mood most of the day, nearly every day

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day

(3) significant weight loss when not dieting or weight gain; or decrease or increase in appetite nearly every day.

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt nearly every day

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Diagnostic criteria for a major depressive episode

A. Five (or more) of the symptoms mentioned above must be present during the same period lasting at least 2 weeks and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

D. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Prevalence and epidemiology

In the Netherlands, approximately 5% of the population aged between 18 and 65 years experiences a major depressive episode during a period of 12 months, representing approximately 545.100 individuals. This prevalence is higher in women (6%) than in men (4%) and decreases with age (41). The prevalence in the Netherlands is comparable to that in other Western European countries and somewhat lower than that in the US (42, 43).

Depression is a temporal mood state with a chronic course. Depressive episodes can occur more than once in a lifetime. The chance of developing a depressive episode becomes higher with increasing number of previous depressive episodes. In addition, individuals with more previous episodes have a higher chance of developing a new episode in the absence of a stressor. Thus it seems that individuals with more previous depressive episodes are more sensitive to develop new depressive episodes (44).

Treatment for depression

The most widely used types of treatment for depression are psychotherapy and pharmacotherapy. Psychotherapies generally aim to restructure cognitions, improve coping styles and maintaining social support of the patient, whereas pharmacotherapies target at the biological pathways that were found to underlie depression. Some examples of psychotherapy are problem solving treatment (aimed at improving coping styles), behavioral activation (increasing the level of activities), cognitive therapy (aimed to improve cognitive flexibility), and interpersonal therapy (aimed to detect and improve problems in interactions with other people). Several types of pharmacotherapies for depression exist, including selective serotonin reuptake inhibitors, tricyclids, and monoamine oxidase inhibitors, and most of these target at improving the serotonergic and noradrenergic neurotransmission.

Other types of treatment or therapies for depression include behavioral activation, physical exercise or running therapy, music therapy, and light therapy. Which treatment a patient should get depends on the severity and duration of the depressive episode, whether the patient has a history of depression, the treatment preference of the patient, the outcomes of earlier

treatments for depression, the presence of other mental or somatic health problems (co-morbidities), expected adverse effects from the treatment, and other intended effects of the treatment such as improving sleep (45). In case of insufficient improvements in the depression, the treatment can be intensified (i.e. increasing dosage), changed to another treatment, or supplemented by another treatment. Thus, what kind of depression treatment is given and with what intensity differs between patients. When the depression has improved sufficiently after the treatment, a relapse prevention treatment module can be added.

Factors associated with depression

In addition to the psychological and biological factors that play a role in the pathway to depression and vulnerability to stressful life events, depression has been found to be associated with several demographical, behavioral and medical characteristics. A higher prevalence of depression is present in individuals with low education, who do not live with a partner, who are unemployed, and have low income (41). Compared to non-depressed individuals, depressed individuals keep an unhealthier lifestyle including smoking and less physical activity (46-48). Depression is associated with a whole range of chronic medical illnesses including diabetes, chronic obstructive pulmonary disease, metabolic syndrome, and cardiovascular disease (49-57). In patients with chronic medical illnesses, depression is associated with stronger disease severity, higher medical symptom burden, more functional impairments, medication non-adherence, and poor health outcomes (58-65).

Depression after a heart attack

The prevalence of major depression during the first month after MI is about 20% (55). This is remarkably higher than in the general population, where the twelve-month prevalence of major depression is approximately 5% (41-43). Depressed MI patients have about 2 to 2.5 times increased risk of new cardiac events or mortality after the MI than non-depressed MI-patients (63). Many potential mechanisms underlying the poor prognosis associated with depression have been identified. Generally, these factors are associated with depression as well as the clinical course of the heart disease and statistical adjustment for these factors attenuates the strength of the association between depression and prognosis. Biological mechanisms potentially underlying the poor prognosis associated with depression include inflammatory activation, a decreased heart rate variability, increased blood platelet activation, dysregulation of the hypothalamus pituitary adrenal axis, and dysfunction in serotonin metabolism and transmission (66). Behavioral mechanisms include physical inactivity (67), smoking (68), non-adherence to lifestyle modification, cardiac medications and cardiac rehabilitation (62, 69, 70). One other important mechanism that at least partially underlies the poor prognosis in depressed MI patients is a more severe heart disease (57, 58, 63). Which of these potential underlying mechanisms underlies the poor prognosis may differ between patients. Thus, some depressed MI patients may be at increased risk of poor prognosis because they have difficulties in changing their lifestyle whereas for others the reason may be that they have a more severe heart disease and there may also be patients for whom both reasons explain the worse prognosis.

Screening for depression in heart disease patients

In heart disease patients depression is associated with reduced quality of life, greater functional impairments, non-adherence to treatment regimens and cardiac rehabilitation, higher health care costs, and an increased risk of new cardiac events and mortality (63, 69, 71-73). Therefore, it appears of utmost importance that depression in heart disease patients is treated successfully. Several clinical guidelines for heart disease recommend that heart disease

patients should be screened for depression and that the depression should be treated (8, 74-76). Chapter 2 presents a systematic review of the literature to answer the question what the evidence is that screening and treatment for depression in heart disease patients has beneficial outcomes. Chapter 3 presents long-term cardiac outcomes associated with depression treatment for depressed MI patients enrolled in the Myocardial Infarction and Depression Intervention Trial (MIND-IT).

Chapter 2

Depression Screening and Patient Outcomes in Cardiovascular Care

A Systematic Review

Brett D. Thombs, Peter de Jonge, James C. Coyne, Mary A. Whooley, Nancy Frasure-Smith, Alex J. Mitchell, Marij Zuidersma, Chete Eze-Nliam, Bruno B. Lima, Cheri G. Smith, Karl Soderlund, Roy C. Ziegelstein

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Structured Abstract

Context: Several practice guidelines recommend that depression be evaluated and treated in patients with cardiovascular disease, but the potential benefits of this are unclear.

Objective: To evaluate the potential benefits of depression screening in patients with cardiovascular disease by assessing (1) the accuracy of depression screening instruments; (2) the effect of depression treatment on depression and cardiac outcomes; and (3) the effect of screening on depression and cardiac outcomes in patients in cardiovascular care settings.

Data Sources: MEDLINE, PsycINFO, CINAHL, EMBASE, ISI, SCOPUS, and Cochrane databases from inception to May 1, 2008; manual journal searches; reference list reviews; and citation tracking of included articles.

Study Selection: We included articles in any language about patients in cardiovascular care settings that (1) compared a screening instrument to a valid major depressive disorder criterion standard; (2) compared depression treatment with placebo or usual care in a randomized controlled trial; or (3) assessed the effect of screening on depression identification and treatment rates, depression, or cardiac outcomes.

Data Extraction: Methodological characteristics and outcomes were extracted by 2 investigators.

Results: We identified 11 studies about screening accuracy, 6 depression treatment trials, but no studies that evaluated the effects of screening on depression or cardiovascular outcomes. In studies that tested depression screening instruments using a priori-defined cutoff scores, sensitivity ranged from 39% to 100% (median, 84%) and specificity ranged from 58% to 94% (median, 79%). Depression treatment with medication or cognitive behavioral therapy resulted in modest reductions in depressive symptoms (effect size, 0.20-0.38; r^2, 1% - 4%). There was no evidence that depression treatment improved cardiac outcomes. Among patients with depression and history of myocardial infarction in the ENRICHD trial, there was no difference in event-free survival between participants treated with cognitive behavioral therapy supplemented by an antidepressant vs usual care (75.5% vs 74.7%, respectively).

Conclusions: Depression treatment with medication or cognitive behavioral therapy in patients with cardiovascular disease is associated with modest improvement in depressive symptoms but no improvement in cardiac outcomes. No clinical trials have assessed whether screening for depression improves depressive symptoms or cardiac outcomes in patients with cardiovascular disease.

Introduction

Major depressive disorder (MDD) is present in as many as 20% of patients with cardiovascular disease (CVD) (55, 77, 78) and predicts adverse cardiovascular outcomes, even after controlling for other risk factors (57, 78-82). In addition, MDD is a chronic, disabling condition that is associated with poor quality of life (83), functional limitations (72), less favorable self-care behaviors (69), and higher health care costs among patients with CVD (73).

Several clinical guidelines, including the American College of Cardiology and the American Heart Association's guidelines for ST-elevation myocardial infarction (MI) (8), unstable angina/non-ST-elevation MI (84), chronic stable angina (85), CVD secondary prevention in women (86), and a recent American Heart Association science advisory (76) recommend that depression be evaluated or that screening for depression be considered in patients with CVD. However, no systematic reviews have assessed whether evidence supports these recommendations. Recommendations for screening and treatment for depression should be population specific since results from one patient group may not generalize to others (87, 88). Screening tools and cutoff scores that optimize diagnostic accuracy in primary care, for instance, may not be appropriate for patients with CVD since some heart disease symptoms may overlap or be confused with symptoms of depression (82, 89-92).

The objective of this systematic review is to determine whether evidence supports recommendations for systematic screening for MDD in cardiovascular

care settings. We used the analytic framework developed by the U.S. Preventive Services Task Force (87, 88) to develop review questions.

Key Question 1: What is the accuracy of screening instruments for depression in cardiovascular care populations?

Key Question 2: Is treatment of depression in cardiovascular care patients effective in improving (a) depression? (b) cardiac outcomes?

Key Question 3: Is systematic screening for depression more effective than usual care in (a) identifying patients with depression, (b) facilitating treatment of depression, (c) reducing depressive symptoms, or (d) improving cardiac outcomes?

Methods

Search Strategy

Articles for review were identified from the MEDLINE, PsycINFO, CINAHL, EMBASE, ISI, SCOPUS, and Cochrane databases, which were searched from inception to May 1, 2008. Two searches were conducted: (1) the first sought articles that compared a screening instrument with a valid major depressive disorder criterion standard or that assessed the effect of screening on depression identification and treatment rates, depression, or cardiac outcomes, and (2) the second search was for articles that compared the effects of depression treatment on depression or cardiac outcomes with placebo or usual care in a randomized controlled trial. Search terms are available from the corresponding author (BDT). Manual searching was done on reference lists of included articles, cardiovascular care guidelines (8, 84-86), systematic reviews, and 33 selected journals for the July 2007 to May 1, 2008, time frame. We tracked citations of included articles using Google Scholar (93) and surveyed 36 experts, including members of the National Heart, Lung, and Blood Institute Working Group on the Assessment and Treatment of Depression in Patients with Cardiovascular Disease (94) and authors of the included treatment studies,

to seek unidentified published depression treatment trials and to determine if there were any unpublished trials.

Identification of Eligible Studies

Article eligibility criteria were established a priori. Eligible articles were studies with original data that evaluated patients in cardiovascular care settings that were published in any language. Abstracts, letters, editorials, and case series or case reports were excluded. Only published studies were eligible for the query seeking the accuracy of depression screening instruments (key question 1), since the inclusion of data from unpublished studies would have required additional analyses and interpretation outside of the scope of this review. Cardiovascular care was defined based on diagnosis (e.g., MI, congestive heart failure) or intervention (e.g., coronary artery bypass graft surgery). Studies in which patient selection was based on clinical characteristics other than cardiovascular disease were excluded. When multiple articles were published on the same cohort, the most comprehensive article was included. Studies with mixed populations were included if CVD patient data were reported separately.

Screening studies that assessed the accuracy of depression screening instruments (key question 1) were included if they compared a screening instrument with a valid standard, defined as a *Diagnostic and Statistical Manual for Mental Disorders* or *International Classification of Diseases* diagnosis of MDD based on a validated diagnostic interview procedure, and if they reported data allowing determination of sensitivity and specificity, positive predictive value, and negative predictive value. Examples of validated interviews include the Structured Clinical Interview for *DSM-IV* (95), the Composite International Diagnostic Interview (96), and the Diagnostic Interview Schedule (38).

Articles assessing the effect of depression treatment on depression and cardiac outcomes (key question 2) included randomized controlled trials with placebo or usual care controls that evaluated pharmacological, psychotherapeutic, or other interventions for MDD among patients in cardiovascular care settings. Only studies with MDD diagnosed using a validated psychiatric interview and *Diagnostic and Statistical Manual for Mental Disorders* or *International Classification of Diseases* criteria were included.

Eligible articles assessing the effect of screening on depression and cardiac outcomes in patients in cardiovascular care settings (key question 3) included randomized controlled trials and prospective studies that compared depression identification, depression treatment rates, depressive outcomes, or cardiac outcomes between CVD patients who underwent depression screening and CVD patients who did not undergo screening.

Two investigators reviewed articles for eligibility independently. Translators were used to evaluate non-English titles, abstracts, and articles. If either reviewer deemed an article potentially eligible based on title or abstract review, then a full-text article review was completed. Disagreement between reviewers after full-text review was resolved by consensus. Chance-corrected agreement between reviewers was assessed with the Cohen kappa statistic.

Evaluation of Eligible Studies

Investigators independently extracted and entered into a standardized spreadsheet data and outcomes. Discrepancies were resolved by consensus. The authors of 1 screening (97) and 1 treatment study (98) provided data to correct minor inconsistencies in original publications. Authors of two studies (99, 100) provided data not included in the original report, which allowed investigators to calculate results not reported in the corresponding studies. Authors of 5 studies (101-105) verified whether diagnoses of MDD were conducted blind to screening results. The author of 1 study clarified the threshold used to diagnose depression (104).

Quality rating was based on methods developed by the US Preventive Services Task Force (88, 106). Ratings reflected the quality of each study relative to our key questions rather than general quality per se. For the question of whether a study assessed the accuracy of depression screening instruments (key question 1), rated items included the relevance and availability of screening tests, the credibility of the reference standard, whether the diagnosis of MDD was made blind to screening results, the spectrum of patients included, sample size, and the screening test reliability. We rated sample size based on the number of patients with MDD in each study (poor, 0–24; fair, 25–99; good, 100 or more). Studies with fewer than 10 patients with depression were rated poor

for overall quality regardless of ratings in other categories. Quality ratings of randomized controlled trials (key question 2) considered the establishment and maintenance of comparable groups, differential or high overall loss to follow-up, clarity of intervention definition, completeness of outcome variables, sample size, and analysis considerations. Study quality was assessed by 2 investigators with discrepancies resolved by consensus.

In studies that assessed the accuracy of depression screening instruments (key question 1), for each screening instrument, sensitivity, specificity, positive predictive value, and negative predictive value with 95% confidence intervals (CIs) are presented (107). Eligible studies were evaluated to determine whether data were sufficiently similar to warrant pooling of results. Substantive heterogeneity between studies was found with respect to cardiovascular diagnoses, criterion standards, and screening instruments and scoring thresholds for depression. Notably, some studies used a priori defined scoring thresholds from the research literature, whereas others used sample-specific thresholds based on receiver operator characteristic (ROC) curves. The latter methods tend to yield overly optimistic estimates of screening accuracy that do not replicate consistently (108). For these reasons, it was determined that data pooling was not appropriate.

For studies that assessed the effect of depression treatment on depression and cardiac outcomes (key question 2), in which multiple depression outcomes were reported, designated primary outcomes for each study were given highest priority. Then observer-rated scales were prioritized over self-report measures. Treatment effect sizes are typically reported as Cohen's *d* (109) or Hedges's g statistic (110), which represent a standardized difference between 2 means. Rosenthal, et al (111, 112) have pointed out, however, that these effect size metrics are nonintuitive and often misunderstood. They recommend using correlation (*r*) metrics that are more easily interpretable. Estimates of *g* or *d* and correlation estimates are essentially equivalent and readily converted from one to another (111, 112). To facilitate interpretation of treatment effect sizes, both Hedges's g and r^2, the percent of variance in depression change scores due to treatment, are reported. Eligible treatment studies were evaluated to determine the appropriateness of pooling results. Studies that assessed the effect of depression treatment on depression and

cardiac outcomes (key question 2) consisted of a small number of heterogeneous studies, each of which used a different therapeutic intervention. Thus, it was determined that data pooling was not appropriate, and studies were reported qualitatively.

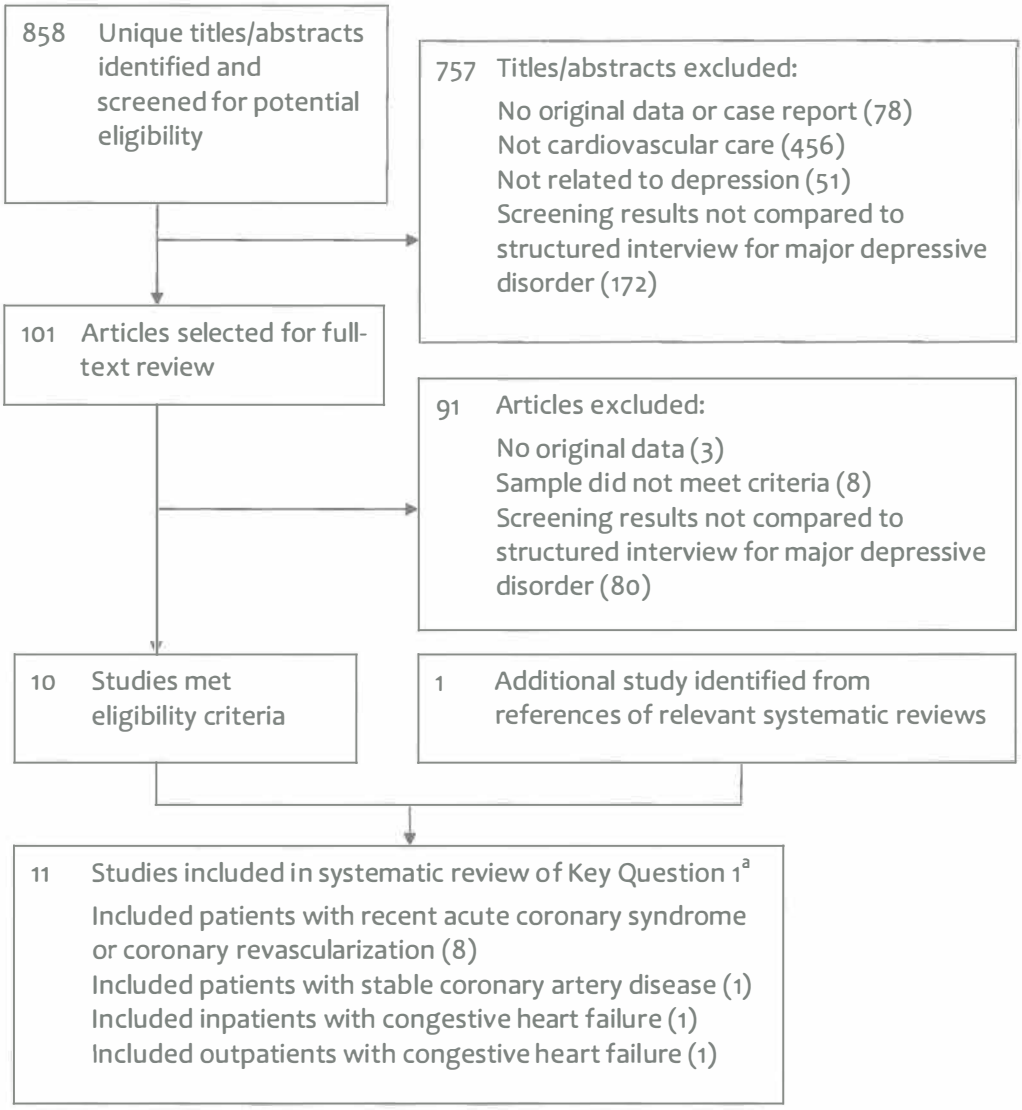
Results

Diagnostic Accuracy of Depression Screening Tools in Cardiovascular Care Settings (Key Question 1)

The literature search for studies that assessed the accuracy of depression screening instruments and the effect of screening on depression and cardiac outcomes in patients in cardiovascular care settings (key questions 1 and 3) yielded 858 unique citations. Of these, 101 were selected for full-text review for key question 1. All but 10 (97, 101-103, 105, 113-117) were excluded because of ineligible patient populations; lack of depression screening tool, a structured interview, or both; or lack of data permitting analyses of diagnostic accuracy. One additional study was identified from the references of a systematic review (104), resulting in 11 articles (**Figure 1**). The kappa for inter-rater agreement was 0.84.

Details of the 11 studies are presented in **Table 1**. Participants in these studies were patients with a recent acute coronary syndrome or coronary revascularization (8 studies) (97, 101, 104, 105, 114-117), stable coronary artery disease (1 study) (103), and hospitalized patients with congestive heart failure (1 study) (102) and outpatients (113) with congestive heart failure (1 study). Of the 8 studies of patients with recent acute coronary syndrome or revascularization, depression assessments were performed on hospitalized patients (3 studies) (101, 104, 114) and in patients discharged from the hospital 1 to 3 months previously (5 studies) (97, 105, 115-117).

Figure 1. Selection of Studies Assessing Accuracy of Screening Instruments for Depression in Cardiovascular Care



[a] Key question 1: what is the accuracy of screening instruments for depression in cardiovascular care populations?

Table 1. Summary of Studies of Diagnostic Accuracy of Depression Screening Tools in Cardiovascular Care Settings

Source; Setting[a]	Instrument; Cutoff Score	No. of Patients (% Male)	Mean Age, y	Major Depression Criterion Standard	No. (%) With Major Depression	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value % (95% CI)	Negative Predictive Value % (95% CI)
Inpatient									
Frasure-Smith et al, 1995, 1998; Canada (101, 118)	BDI ≥10[b]	218 (78)	60	Modified DIS[c]	33 (15)	82 (66 - 91)	78 (71 - 83)	40 (29 - 52))	96 (92 - 98)
Freedland et al, 2003; United States (102)	BDI ≥10[b]	613 (49)	66	Modified DIS[d]	120 (20)	88 (80 - 92)	58 (54- 63)	34 (29 - 39)	95 (92 - 97)
Dickens et al, 2004; Great Britain (104)	HADS ≥17[e]	314 (63)	58	SCAN	65 (21)	88 (78 - 94)	85 (80 - 89)	60 (50 - 69)	96 (93 - 98)
Huffman et al, 2006; United States (114)	2-items from BDI[e]	131 (80)	62	SCID-IV	17 (13)	94 (73 - 99)	76 (68 - 83)	37 (24 - 52)	99 (94 - 100)
Outpatient									
Gutierrez, 1999; Canada (113)	BDI ≥13[b]	40 (50)	70	SCID-IV	6 (15)	83 (44 - 97)	94 (81 - 98)	71 (36 - 92)	97 (85 - 99)
Strik et al, 2001, the Netherlands (97)[f]	BDI ≥10[b]	196 (77)	60	SCID-IV	22 (11)	82 (61 - 93)	79 (72 - 84)	33 (22 - 46)	97 (93 - 99)
	HADS ≥13[e]	179 (77)			20 (11)	90 (70 - 97)	84 (78 - 89)	42 (28 - 57)	99 (95 - 100)
	HADS-D ≥4[e]	179 (77)			20 (11)	85 (64 - 95)	75 (68 - 81)	30 (20 - 43)	98 (93 - 99)
	SCL-90-D ≥25[e]	195 (76)			22 (11)	95 (78 -99)	74 (67 - 80)	32 (22 - 44)	99 (96 - 100)
McManus et al, 2005; United States (103)	CES-D-10 ≥10[b]	1024 (82)	67	DIS	224 (22)	76 (70-81)	79 (76 - 82)	50 (45 - 56)	92 (90 - 94)
	PHQ-9 ≥10[b]					54 (47 - 60)	90 (88 - 92)	60 (53 - 67)	87 (85 - 90)
	PHQ-2 ≥3[b]					39 (33 - 45)	92 (90 - 94)	58 (50 - 65)	84 (82 - 87)
	2-item yes/no[b]					90 (86 - 93)	69 (66 - 72)	45 (40 - 50)	96 (94 - 97)
Denollet et al, 2006; the Netherlands (105)	SAD4 ≥3[g]	176 (76)	60	SCID-IV	20 (11)	95 (76 - 99)	68 (60 - 75)	28 (18 - 39)	99 (95 - 100)

Low and Hubley, 2007; Canada (116)	BDI-II ≥14[b] GDS ≥11[b]	119 (75)	63	SCID-IV	7 (6)	86 (49 - 97) 100 (65 - 100)	89 (81 - 93) 85 (77 - 90)	33 (16 - 56) 29 (15 - 49)	99 (94 - 100) 100 (96 - 100)
Stafford et al, 2007; Australia (115)[h]	HADS-D ≥6[e] PHQ-9 ≥6[e]	193 (81)	64	MINI	35 (18)	80 (64 - 90) 83 (67 - 92)	82 (75 - 87) 78 (71 - 84)	49 (37 – 62) 46 (34 - 58)	95 (90 - 97) 95 (90 - 98)
Frasure-Smith et al, 2008; Canada (117)	BDI-II ≥14[b] HADS-A ≥8[b]	804 (81)	60	SCID-IV	57 (7)	91 (81 - 96) 84 (73 - 91)	78 (74 - 80) 62 (58 - 65)	24 (19 - 30) 14 (11 - 19)	99 (98 - 100) 98 (96 - 99)

Abbreviations: BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; CES-D-10, Center for Epidemiological Studies Depression Scale, 10-item version; CI, confidence interval; DIS, Diagnostic Interview Schedule; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale, total score; HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, depression subscale; MINI, Mini International Neuropsychiatric Interview; PHQ-2, Patient Health Questionnaire-2; PHQ-9, Patient Health Questionnaire-9; SAD4, Symptoms of Anxiety-Depression index; SCAN, Schedule for Assessment of Neuropsychiatric Disorders; SCID-IV, structured clinical interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; SCL-90-D, depression subscale of the Symptom Checklist 90.

[a] Diagnoses were post-acute myocardial infarction in Frasure-Smith et al 1995, 1998 (101, 118), Strik et al (97), Dickens et al (104), Denollet et al (105), and Huffman et al (114); congestive heart failure in Gutierrez (113) and Freedland et al (102); coronary artery disease in McManus et al (103); post-acute coronary syndrome in Low and Hubley (116) and Frasure-Smith et al 2008 (117); and post-acute myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty in Stafford et al (115).

[b] Cutoff derived from the literature.

[c] The modified DIS did not require that symptoms be of at least 2 weeks' duration and did not apply the criteria of seeking medical help and experiencing impairment.

[d] The depression section of the modified DIS starts with somatic rather than cognitive or mood-related symptoms and focuses on current rather than lifetime symptoms.

[e] Cutoff derived from receiver operating characteristic curve.

[f] The number of patients administered each screening tool and diagnostic data were provided by the authors of the original study to correct minor inconsistencies in the published
manuscript.

[g] Cutoff derived from upper tertile.

[h] Diagnoses for Stafford et al (115) also include CABG or PTCA.

Six studies (101-103, 113, 116, 117) used prespecified thresholds to define depression, 1 used a threshold based on the upper tertile of scores (105), and 4 used ROC curve methods to identify thresholds that optimized accuracy (97, 104, 114, 115). Frasure-Smith et al (101, 118) and Strik et al (97) each reported sensitivity and specificity close to 80% for a Beck Depression Inventory score of 10 or greater in post MI patients, whereas Freedland et al (102) reported good sensitivity (88%), but poor specificity (58%), with the same threshold among hospitalized patients with congestive heart failure. Frasure-Smith et al (117) and Low and Hubley (116) reported good sensitivity (91% and 86%, respectively) and specificity (78% and 89%, respectively) for a Beck Depression Inventory-II score (119) of 14 or greater in outpatients after acute coronary syndrome. Prespecified thresholds performed reasonably well for a 10-item version of the Center for Epidemiological Studies Depression Scale (120), the Patient Health Questionnaire-9 (121, 122), the Patient Health-Questionnaire-2 (123), a 2-item yes/no screening tool (124), and the Geriatric Depression Scale (125). McManus et al (103), however, found that recommended cutoffs from primary care for the Patient Health Questionnaire-2 (≥3) and Patient Health Questionnaire-9 (≥10) resulted in good specificity (92% and 90%, respectively), but poor sensitivity (39% and 54%, respectively) in patients with coronary artery disease.

Stafford et al (115) used sample-specific ROC curve methods and found that a lower threshold of 6 or greater on the Patient Health Questionnaire-9 optimized sensitivity (83%) and specificity (78%) among coronary artery disease outpatients. Sensitivity in studies that used sample-specific ROC curve analyses ranged from 80% to 95%, and specificity from 74% to 85% (97, 104, 114, 115). Two separate studies (97, 104) performed ROC curve analyses with the 14-item Hospital Anxiety and Depression Scale (126). The 2 studies reported similar sensitivity (90% and 88%) and specificity (84% and 85%), but an optimal Hospital Anxiety and Depression Scale score was reported to be 13 or greater in one (97) and 17 or greater in the other (104).

The quality of 4 studies was good (101-103, 117), 5 studies were fair (97, 104, 105, 114, 115), and 2 studies were poor (113, 116). All studies were rated good for administering an appropriate screening tool and for using a credible reference standard except for 1 study (115), that used the Mini International Neuropsychiatric Interview administered by telephone as its criterion standard.

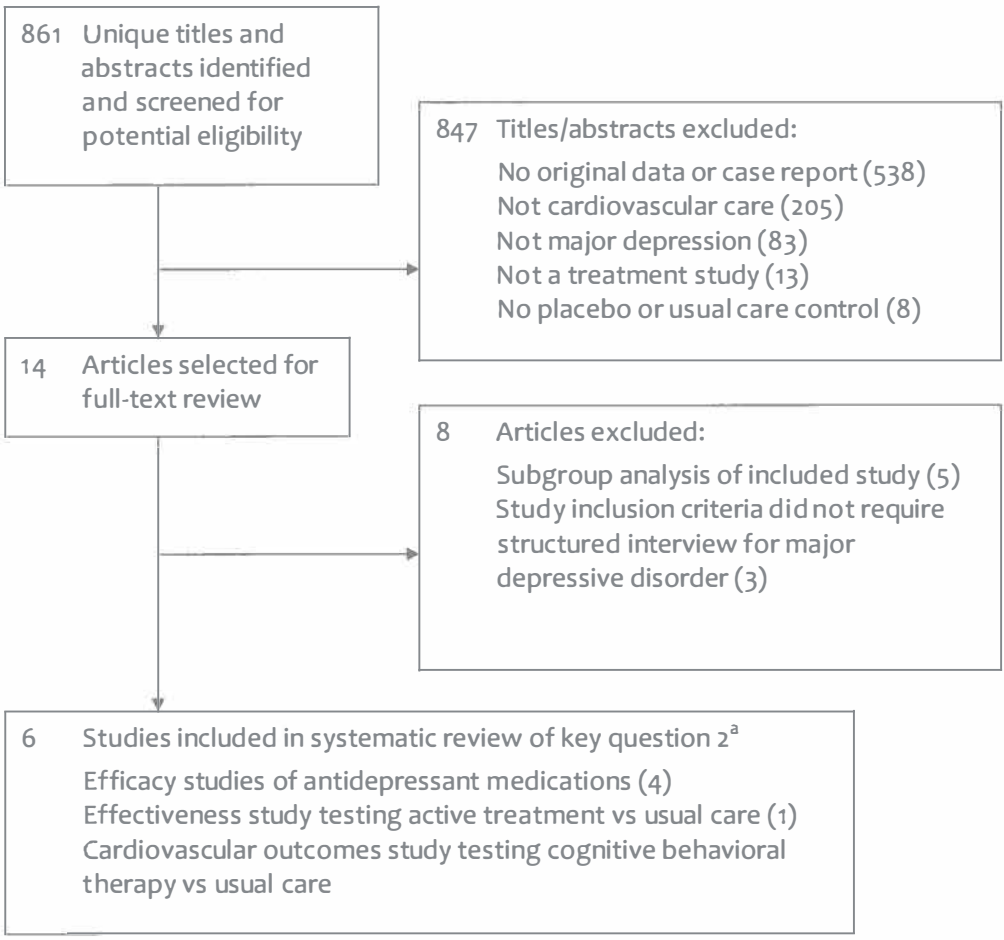
One study was rated poor for administration of a reliable screening test because patients returned screening questionnaires by mail. The delay between Structured Clinical Interview for *DSM-IV* assessments and questionnaire return was more than 2 weeks in some cases (97).

In summary, for tests of a priori screening thresholds (including studies in which more than 1 instrument was administered), sensitivity ranged from 39% to 100% (median, 84%), and specificity from 58% to 94% (median, 79%). There were few examples of demonstrated accuracy with screening tools or depression thresholds that were tested in more than 1 sample of cardiovascular care patients. No studies addressed potential harms of screening, including false-positive results, the cost and inconvenience of additional follow-up assessments, the adverse effects and costs associated with treating incorrectly diagnosed patients, or inappropriate labelling (106).

The Effects of Depression Treatment in Cardiovascular Care Patients (Key Question 2)

For assessing the effect of depression treatment on depression and cardiac outcomes (key question 2), there were 861 unique citations and 14 articles selected for full-text review. Six of these met inclusion criteria (Figure 2) (98-100, 127-129). No unpublished trials were identified. The kappa for inter-rater agreement was 0.86.

Figure 2. Selection for studies Assessing Effectiveness of Depression Treatment on Depression and Cardiac Outcomes in Cardiovascular Care patients



[a] Key question 2: is treatment for depression in cardiovascular care patients effective in improving (a) depression; (b) cardiac outcomes?

Details of the 6 studies are presented in Table 2 and Table 3. There were 4 efficacy studies of antidepressant medications, including 1 each using fluoxetine (127), sertraline (128), citalopram (129), and mirtazapine (98). Strik et al (127) compared the efficacy and safety of fluoxetine administered to patients after their first MI. The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) (128) tested the efficacy and safety of sertraline in patients with unstable ischemic heart disease. The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial (129) was a parallel-group, 2 x 2 factorial trial that compared citalopram to placebo and compared short-term interpersonal psychotherapy plus clinical management to clinical management alone in patients with coronary artery disease. Honig et al (98) compared mirtazapine to placebo for 8 weeks in post-MI patients, then offered open treatment with citalopram in the case of insufficient response. The original report on the mirtazapine trial did not note that open label treatment was introduced at 8 weeks and presented results for both 8 and 25 weeks. Only data at 8-week follow-up were included for this review. The Honig et al trial was conducted as part of the treatment group of the Myocardial Infarction and Depression – Intervention Trial (MIND-IT) (100). MIND-IT was an effectiveness study because rather than testing the efficacy of a single treatment under optimal conditions, it investigated whether implementing any active treatment strategy resulted in better outcomes compared with usual care (130). Treatment options for patients included mirtazapine or placebo as part of the double-blind Honig et al trial (98), open treatment with citalopram, and tailored treatment at the discretion of the treating psychiatrist. The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial examined the effects of cognitive behavioral therapy plus adjunctive sertraline treatment in the case of insufficient response on depression and cardiac outcomes in post-MI patients (99).

Table 2. Diagnoses and Timing for Randomized Controlled Trials of Pharmacological or Psychotherapeutic Treatment of Depression in Cardiovascular Care Settings

Source	Setting	Diagnosis	Timing of depression assessment[a]	Treatment duration, wk	Cardiovascular Follow-up duration[b]
			Efficacy		
Strik et al, 2000 (127)	The Netherlands	Post-AMI	3-12 mo	25	25 wk
Glassman et al, 2002 (128) [c]	United States, Canada, Europe, Australia	Post-ACS	1st ≤ 30 d followed by 2nd assessment after 2-wk placebo run-in	24	24 wk
Honig et al, 2007 (98)	The Netherlands	Post-AMI	3-12 mo	8[d]	24 wk
Lespérance et al, 2007 (129) [e]	Canada	CAD	NA	12	12 wk
			Effectiveness		
Van Melle et al, 2007 (100) [f]	The Netherlands	Post-AMI	3-12 mo	24	6-15 mo
			Cardiovascular Outcomes		
Berkman et al, 2003 (99) [g]	United States	Post-AMI	≤ 28 d	26[h]	18-48 mo

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; NA, not applicable.

[a] Denotes timing after occurrence of acute event.

[b] Denotes duration for cardiovascular events following randomization.

[c] Denotes the Sertraline Antidepressant Heart Attack Randomized (SADHART) trial.

[d] Outcomes at 8 weeks were reviewed instead of 24-week results because 8 weeks open treatment with citalopram was offered in the case of refusal or insufficient treatment response (98).

[e] Denotes the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial.

[f] Denotes the Myocardial Infarction and Depression-Intervention (MIND-IT) trial.

[g] Denotes the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial.

[h] Maximum duration of the cognitive behavioral therapy intervention was 6 mo. Group therapy could extend 12 additional weeks and adjunctive sertraline treatment for up to 12 mo.

Despite substantial differences in design, the 4 efficacy studies reported consistently positive but modest effects on depression. Effect sizes for primary outcome measures ranged from 0.20 to 0.38 (r^2, 1% - 4%). The number needed to treat for response ranged from 5 to 8 (127, 129) and for remission from 6 to 9 (98, 127). In the ENRICHD trial (99), the effect size of cognitive behavioral therapy supplemented with adjunctive sertraline when indicated was 0.22 (r^2, 1%). However, 13% of patients in the usual care group were prescribed an antidepressant medication by 6 months. Only the ENRICHD (99) and MIND-IT (100) studies were designed to assess cardiovascular outcomes, although the MIND-IT study had very low statistical power. Neither found evidence that depression treatment affects cardiac outcomes. Among patients with depression and a history of MI in the ENRICHD clinical trial, there was no difference in event-free survival between participants treated with cognitive behavioral therapy supplemented by an antidepressant vs usual care (75.5% vs 74.7%). Cardiac event-free survival in the MIND-IT trial was 86.2% for patients in the treatment group and 87.3% for patients in the control group. Among the 6 treatment studies, 3 were rated as good (99, 128, 129) and 3 were rated as fair-good (98, 100, 127). Characteristics that limited quality were nonblinding of patients for psychotherapeutic treatments (99, 100), unequal distribution of confounders (98), differential loss to follow-up (98, 99, 127), use of last observation carried forward to impute missing data (98, 127), and small sample sizes (98, 127). The MIND-IT study (100), which was rated fair-good overall, was an effectiveness study and not designed to evaluate treatment efficacy.

In summary, effect sizes for treatment of depression in the 4 efficacy studies and the ENRICHD trial were modest. All trials reviewed met or exceeded the 6- to 8-week duration that is typical in acute phase trials of antidepressant agents (131, 132). However, none continued treatment or assessed follow-up long enough to determine whether antidepressant use reduces the risk of relapse or recurrence in cardiac patients who respond to acute treatment (133). Only 2 studies had follow-up periods that were long enough to assess cardiac outcomes (99, 100). Neither found evidence of an effect of depression treatment. Two studies reported that selective serotonin reuptake inhibitors did not affect cardiac function (127, 128), but no studies assessed other potential harms, such as medication side effects (106).

Table 3. Outcomes for Randomized Controlled Trials of Pharmacological or Psychotherapeutic Treatment of Depression in Cardiovascular Care Settings[a]

		No. (%), OR (95% CI)			Hedges g (95% CI), r^2_1, %	
Efficacy						
Source	No. Randomized[b]	Depression Remission[c,d]	Depression Response[c,e]	Cardiovascular With Outcome (%)[f]	Depression Primary[c]	Depression Secondary[c]
Strik et al, 2000 (127)	Fluoxetine 27 Placebo 27	7 (26) 4 (15) 2.01 (0.51-7.90)	13 (48) 7 (26) 2.65 (0.84-8.34)	1 (4) 6 (22) 0.13 (0.02-1.21)	Δ HAMD-17 0.38 (-0.16 to 0.92), 4	NA
Glassman et al, 2002 (128)[g]	Sertraline 186 Placebo 183	NA NA	125 (67) 97 (53) 1.82 (1.19-2.77)	32 (17) 41 (22) 0.72 (0.43-1.21)	CGI-I 0.20 (0.00 to 0.41), 1	Δ HAMD-17 0.14 (-0.06 to 0.35), 1[h]
Honig et al, 2007 (98)	Mirtazapine 47 Placebo 44	16 (34) 7 (16) 2.73 (1.00-7.48)	27 (57) 18 (41) 1.95 (0.85-4.49)	8 (17) 10 (23) 0.70 (0.25-1.97)	Δ HAMD-17 0.35 (-0.06 to 0.77), 3	Δ BDI 0.50 (0.08 to 0.91), 6 Δ SCL-90-D 0.53 (0.11 to 0.95), 7 Δ CGI-S 0.83 (0.40 to 1.26), 15 CGI-I 0.30 (-0.11 to 0.72), 2
Lespérance et al, 2007 (129)[i]	Citalopram 142 Placebo 142	51 (36) 32 (23) 1.93 (1.14-3.25)	75 (53) 57 (40) 1.67 (1.04-2.67)	6 (4) 6 (4) 1.00 (0.32-3.18)	Δ HAMD-24 0.33 (0.10 to 0.56), 3	Δ BDI-II 0.34 (0.10 to 0.57), 3 Δ HAMD-17 0.29 (0.05 to 0.52), 2
	IPT and CM 142 CM only 142	40 (28) 43 (30) 0.90 (0.54-1.51)	61 (43) 71 (50) 0.75 (0.47-1.20)	9 (6) 3 (2) 3.14 (0.83-11.83)	Δ HAMD-24 -0.23 (-0.46 to 0.00), 1	Δ BDI-II 0.10 (-0.13 to 0.34), <1 Δ HAMD-17 -0.22 (-0.46 to 0.01), 1
Effectiveness						
Van Melle et al, 2007 (100)[j]	Treatment 209 Usual care 122[k]	91/132 (69) 58/86 (67) 1.11 (0.62-1.99)	NA	27 (14) 15 (13) 1.10 (0.56-2.16)[l]	BDI 0.12 (-0.15 to 0.39), <1	NA

			Cardiovascular outcomes			
Berkman et al, 2003 (99) [l]	CBT 925 Usual care 909	NA	NA	227 (25) 230 (25) 0.96 (0.81 – 1.17) 128 (14) 129 (14) 0.97 (0.76-1.24)	Δ HAMD-17 0.22 (0.11 to 0.33), 1	Δ BDI 0.31 (0.20 to 0.42), 2

Abbreviations: BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; CBT, Cognitive behavioral therapy; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; CI, confidence interval; CM, Clinical Management; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMD-24, 24-item Hamilton Depression Rating Scale; IPT, Interpersonal psychotherapy; NA, not applicable; OR, odds ratio; SCL-90-D, depression subscale of the Symptom Checklist 90.

[a] Baseline HAMD-17 scores, mean (SD) are: 21.6 (3.6) for Strik et al (127); 19.6 (5.4) for Glassman et al (128); 17.8 (not reported) for Honig et al (98); 22.8 (5.1) for Lespérance et al (129); and 17.7 (6.4) for Berkman et al (99).

[b] Point at which treatment and control groups are defined.

[c] All reported depression outcomes were assessed at the end of the treatment period except van Melle et al (100) in which depression outcomes were assessed 18 months post-AMI (0-9 mo after completion of treatment).

[d] Remission defined by Strik et al (127) as a HAMD-17 score lower than 7, by Honig et al (98) as a HAMD-17 score of 7 or lower, by Lespérance et al (129) as a HAMD-24 score of 8 or lower, and van Melle et al (100) did not describe remission criteria. Results shown for van Melle et al (100) reflect the percentage of patients who no longer met *International Classification of Diseases, 10th Revision* criteria for depressive disorder among those who were assessed (132 patients [63%] in the intervention group and 86 patients [65%] in the usual care group [calculated from original data]).

[e] Response defined by Strik et al (127) as a 50% or greater reduction in HAMD-17 scores, by Glassman et al (128) as a GCI-I score of 1 or 2 (very much or much improved), by Honig et al (98) as a 50% or greater reduction in HAMD-17 scores or a HAMD-17 score of 9 or lower, by Lespérance et al (129) as a 50% or greater reduction in HAMD-24 scores.

[f] Cardiovascular outcomes are cardiac hospitalization for Strik et al (127); major adverse cardiac events (those involving death or requiring hospitalization) for Glassman et al (128); hospitalization for Honig et al (98); cardiovascular serious adverse events (myocardial infarction, congestive heart failure, worsening angina, stroke, or other cardiovascular events) for Lespérance et al (129); total cardiac events (cardiac death, recurrent myocardial infarction, revascularization, heart failure, myocardial ischemia, and ventricular arrhythmia [17 patients were lost to follow-up: treatment group, 196; usual care, 118]) for van Melle et al (100); recurrent myocardial infarction or death from any cause and death for Berkman et al (99).

[g] Denotes the Sertraline Antidepressant Heart Attack Randomized (SADHART) trial.

[h] Patients were assessed with HAMD-17 at 16 weeks, but not 24 weeks.

[i] Denotes the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial.

[j] Denotes the Myocardial Infarction and Depression-Intervention (MIND-IT) trial.

[k] No. randomized patients in Lespérance et al, (129) denotes a 2_2 factorial design with 284 total patients.

[l] Denotes the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial.

Effects of Depression Screening on Outcomes in Cardiovascular Care Patients (Key Question 3)

Of the 858 unique citations identified in the search for studies that assessed the accuracy of depression screening instruments (key question 1) or the effect of screening on depression and cardiac outcomes in patients in cardiovascular care settings (key question 3), 66 articles were selected for full-text review for key question 3. No articles met eligibility criteria, and no unpublished studies were identified.

Comment

Several clinical guidelines for cardiovascular care (8, 84, 86) recommend that depression be evaluated or that screening for depression be considered in patients with CVD. Whether depression screening is of benefit to patients with CVD is unknown. Our systematic review of the evidence shows that depression screening tools are reasonably accurate in patients with CVD, but there are few examples of screening tool thresholds with demonstrated accuracy in more than 1 sample of patients with CVD. There is evidence that depression treatment in patients with CVD improves depression, but the effects on depression are modest with only minimal benefit compared to usual care or placebo. There is no evidence that depression treatment reduces cardiovascular events. No studies have examined whether screening for depression in patients with CVD improves access to depression care or outcomes.

Among the studies that tested depression screening instruments using a priori thresholds, the ranges of sensitivity (39% - 100%; median, 84%) and specificity (58% - 94%; median, 79%) were similar to those reported in a systematic review of case-finding instruments in primary care in which sensitivity ranged from 50% to 97% (median, 85%) and specificity from 51% to 98% (median, 74%) (134). However, given the high false-positive rate of screening tools, a clinical interview is necessary to establish a diagnosis of depression. Based on the 15% median prevalence of MDD we identified in the depression

screening studies (Table 1), along with the median sensitivity (84%) and specificity (79%) of the depression screening tools, 1000 depression screenings would result in 304 patients needing further evaluation of whom 126 (41% of those who screen positive) would have MDD. Thus, the adoption of depression screening in patients with CVD would consume substantial resources and might identify problems that are ultimately not highly amenable to intervention in a cardiovascular care settting (135). If antidepressant therapies are prescribed by cardiologists based on a screening tool alone without a follow-up clinical interview to establish a diagnosis of MDD, then potentially dangerous overtreatment and mislabeling could occur.

We found that effect sizes for drug treatment trials were consistently positive, but generally small (0.20-0.38; 1%-4% of the variance in depression change scores). The mean baseline 17-item Hamilton Depression Rating Scale scores in drug trials we reviewed were generally several points lower than baseline 17-item Hamilton Depression Rating Scale scores of trials submitted to the U.S. Food and Drug Administration for licensing, and lower baseline scores have been shown to be associated with smaller responses to drug therapy (131, 132). However, effect sizes in patients with CVD were similar to effect sizes for the same agents from all published and unpublished studies registered with the U.S. Food and Drug Administration as reported by Turner et al (136) (0.24-0.35; r^2, 1%-3%; Figure 3). Effect size was similarly small for cognitive behavioral therapy in the ENRICHD trial (0.22) and was negative and nonsignificant for interpersonal psychotherapy in the CREATE trial. Our review included only two non-drug treatment trials because existing psychological and behavioral interventions studied in cardiovascular care settings have not been randomized controlled trials or have not specified MDD as an inclusion criterion (137-139). Given the relatively small effect sizes for depression treatment outcomes identified in our review, it is not surprising that no evidence was found for improved cardiovascular outcomes.

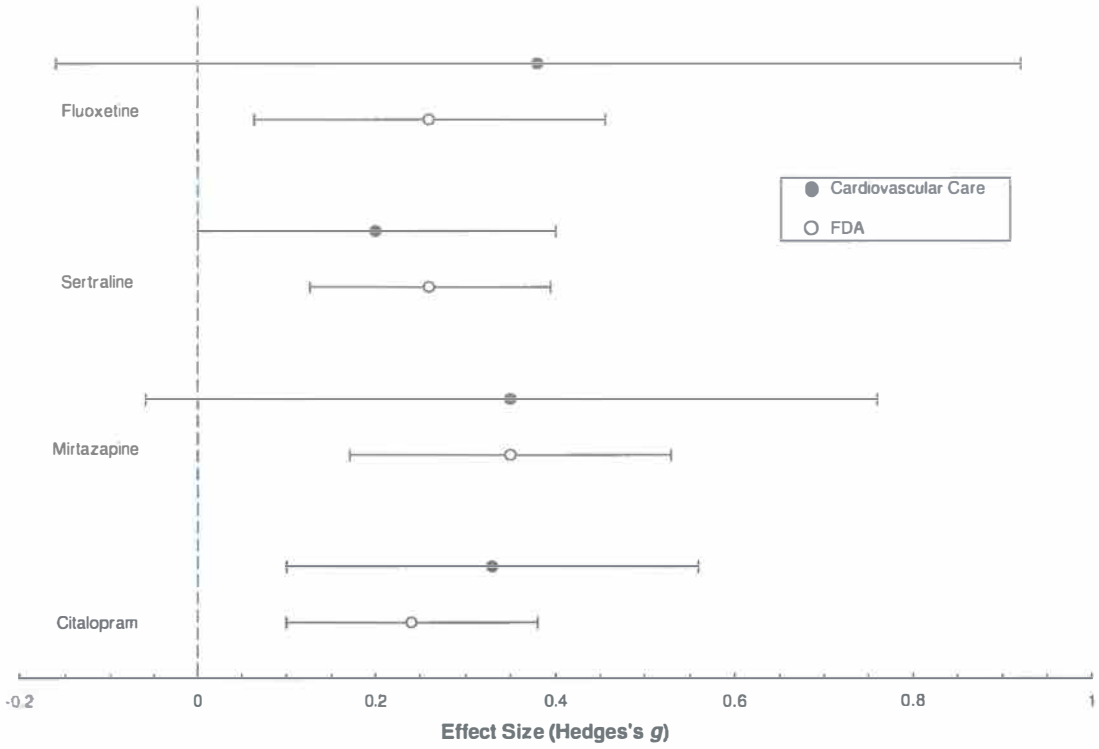


Figure 3. Comparison of Effect Sizes for Pharmacological Interventions in Cardiovascular Care and in Studies Registered with the FDA (136)

FDA indicates U.S. Food and Drug Administration. The numbers of FDA studies are from published and unpublished studies reported by Turner et al and registered with the FDA (fluoxetine: n=5 studies, sertraline: n=5 studies, mirtazapine: n=10 studies, citalopram: n=5 studies from the FDA).

Despite these limitations, depression screening with easy-to-use case-finding instruments to improve the ability of non-mental health specialists to detect and manage depression has substantial appeal (140). In primary care settings, however, the use of depression screening questionnaires without substantial organizational systems to support management and follow-up provides little or no benefit for patients (141, 142). A recent Cochrane systematic review of screening and case-finding in non-mental health settings (141) concluded that screening alone results in a modest increase in the recognition of depression by clinicians, but does not improve depression outcomes.

The greatest challenges to ensuring accurate diagnosis and treatment of depression for cardiac patients may not lie in the efficacy of available screening tools, but in the effectiveness with which treatment can be delivered, given the competing demands when treating patients with CVD. One-quarter to one-third of patients in primary care settings discontinue depression treatment within 1 month of initiation and as many as one-half discontinue treatment within 3 months (143-145). There is little reason to think that the situation would be better in cardiovascular care settings. Collaborative care has been proposed as a potential solution to management barriers that may improve both short- and longer-term depression outcomes (142, 146, 147). Collaborative care is a multifaceted organizational intervention based on chronic disease management principles that involves a greater role of nonmedical specialists (e.g., nurse practitioners or case managers) working with mental health specialists and other clinicians to provide optimal disease management and treatment follow-up (147-150). A recent meta-analysis by Gilbody et al (147), however, found only modest effects on depression outcomes for collaborative care interventions at 6-month (effect size 0.25) and up to 5-year follow-up (effect size 0.15). Although 1 study (150) found that collaborative care was cost-effective for patients with depression and diabetes when total health service costs were considered, more favorable evidence is needed.

In summary, this systematic review of the evidence did not find evidence for or against the recommendations that depression be evaluated or that screening for depression be considered as part of standard care in patients with CVD (8, 84, 86). There was not enough evidence to assess potential harms related to screening or treatment. The high prevalence of depression in patients

with CVD, the adverse health care outcomes associated with depression, and the availability of easy-to-use case-finding instruments make it tempting to endorse widespread depression screening in cardiovascular care. However, the adoption of depression screening in cardiovascular care settings would likely be unduly resource intensive and would not be likely to benefit patients in the absence of significant changes in current models of care. More research on the impact of depression screening in the context of different care models is needed. If collaborative care models were to show, for instance, that the cost of improving depression outcomes could be offset by increased productivity and decreased absenteeism,[81] then depression screening in collaborative care may be justifiable. Finally, although routine depression screening is not supported by the evidence, physicians should be aware that there are patients with serious and potentially life-threatening depression in most cardiovascular care settings. For these patients, physicians should provide appropriate treatment, referral, or both.

Chapter 3

Treatment for depression after myocardial infarction and impact on 8-year risk of subsequent cardiac events and mortality:

a randomized controlled trial

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Submitted

Abstract

Background: Post-myocardial infarction (MI) depression is associated with worse cardiac outcomes.

Aims: Evaluating effects of depression treatment in MI-patients on long-term cardiac outcomes.

Method: Depressed MI-patients (n=331) recruited from 11 hospitals in the Netherlands were randomized to care-as-usual (CAU) or intervention, including pharmacological and non-pharmacological therapy for depression. The primary outcome included cardiac events/cardiac mortality till 8 years after randomization.

Results: Two-hundred-ninety-five patients (187 intervention, 108 CAU) had data on the primary outcome. The intervention did not affect the primary outcome (HR: 0.96 (95% CI: 0.66-1.39)) or all-cause mortality (HR: 0.74 (95% CI: 0.41-1.33)). This was similar for both genders. Treatment-response was not associated with the outcomes. Receiving depression treatment, regardless of randomization-status, reduced all-cause mortality rates (HR: 0.51 (95% CI: 0.27-0.98)).

Conclusions: The intervention did not reduce long-term cardiac morbidity and mortality. Receiving depression treatment increased survival. It remains unclear whether this is due to the treatment itself.

Introduction

Depression after myocardial infarction (MI) is associated with a two-fold increased risk of cardiac morbidity and mortality (63). Therefore, it was hoped that treatment for depression in MI-patients would reduce the risk of cardiac morbidity and mortality.

Unfortunately, large-scale randomized controlled trials (RCT's) in depressed cardiac patients found treatment for depression not to affect cardiac prognosis (151). Subgroup analyses of large RCT's revealed even worse cardiac outcomes associated with a distress-reducing intervention and depression treatment in women, but not in men (99, 152). Furthermore, better cardiac outcomes were found in patients whose depression or psychological distress improved by the treatment or placebo (i.e. ' responders'), compared to those whose depression did not improve (i.e. 'non-responders') (153-155), and in patients who received additional treatment for depression outside the study procedure, compared to those who did not (156).

The present article reports long-term cardiac outcomes up to 8 years after treatment initiation for patients enrolled in the Myocardial Infarction and Depression Intervention Trial (MIND-IT). In a previous publication it was reported that the intervention had no effect on depression and cardiac outcomes up till 18 months after the MI (100). Based on this, the chance that the intervention affects long-term cardiac outcomes is small. In addition to a potential effect of the intervention on long-term cardiac outcomes, the present article evaluates several subgroup analyses based on findings from the other studies. First, it will be evaluated whether the effects of the intervention on cardiac outcomes differs between men and women. Second, it is evaluated whether patients whose depression improved by treatment with antidepressants (i.e. 'responders') have better cardiac outcomes compared to non-responders. And third, the risk of cardiac morbidity and mortality will be compared between patients who received treatment for depression and those who did not.

Method

Design of the study

MIND-IT was a multicenter RCT with the goal to determine the effectiveness of implementing an antidepressant treatment strategy compared to CAU. Details of this study are described before (100, 157). Eligible MI-patients were screened with the Beck Depression Inventory (BDI, (158)) during hospitalization and 3 months later. Those scoring ≥10 at either time point underwent the Composite International Diagnostic Interview (CIDI) version 2.1 (37) at 3 months after the MI to assess the presence of an *International Classification of Diseases* (ICD)-10 diagnosis of a depressive episode after the MI (25). Patients with a diagnosis of a current depressive episode were randomized to the intervention or to CAU. Those who did not meet criteria for a post-MI depressive episode and those who scored <10 on the BDI were assessed for depression again at 6 months post-MI. This was repeated at 9 and 12 months post-MI. Patients with significant suicide risk were not randomized and referred for psychiatric treatment outside the study. Group assignment was carried out at the Trial Coordination Centre in Groningen using computer-generated permuted blocks of four. Randomization was stratified according to study location and timing of depression onset (i.e. within 6 months post-MI versus 6 months or later). Initially, the randomization ratio was 1:1, but because the number of patients actually treated with antidepressants was lower than expected, the randomization ratio was changed to 2:1 (intervention: CAU) on 14 March 2001. The Trial Coordination Centre in Groningen independently performed data management.

Participants

Between September 1999 and November 2002, patients admitted for MI were recruited consecutively from eleven hospitals in the Netherlands. To be included, patients had to meet two of the following criteria: 1) chest pain for at least 20 minutes, 2) typical electrocardiographical changes and 3) a documented increase in cardiac enzyme levels. Patients were excluded if they were unable to participate in study procedures (unable to communicate or not available for

follow-up), had another somatic disease likely to influence short-term survival, already received treatment for depression or were participating in another clinical trial. The institutional review board of each participating hospital approved the protocol and each participant signed informed consent. All participating patients were informed that they were free to seek help for mood problems outside the study protocol, which was recorded.

Intervention

The goal of MIND-IT was to compare cardiac outcomes for depressed MI-patients who were provided optimal treatment for depression in the intervention arm, versus those provided care as usual (CAU) only. To avoid influencing the usual care, feedback about the depression status was given only to patients in the intervention arm and not to patients nor their practitioners in the CAU arm (i.e. a Zelen design: (159)). The kind of treatment was not essential for MIND-IT. Patients allocated to the intervention arm were offered several types of treatment for depression from which they could choose. The first option was to participate in a double-blind placebo-controlled trial on the efficacy of mirtazapine. In case of refusal or no sufficient treatment response after eight weeks, defined as at least 50% reduction in the Hamilton Depression Rating Scale (HDRS; (160)) score or a HDRS-score of <10 at 8 weeks, patients in both arms were offered open treatment with citalopram. The second option was an open treatment protocol with citalopram. The third option was 'tailored treatment', which was at the discretion of the psychiatrist. Monthly visits to the psychiatrist were scheduled and the treatment duration was six months. More details about the intervention can be found in Van den Brink et al. 2002 (157). Patients in the CAU arm were free to seek treatment outside the study protocol, which was recorded.

Baseline variables

Age, sex, smoking status and clinical characteristics were assessed during hospitalization for the index-MI and obtained from medical records. The Charlson Comorbidity Index was calculated to assess a cumulative burden of somatic comorbidity. Left ventricular ejection fraction (LVEF) was assessed by

echocardiography, radionuclide ventriculography, gated single photon emission computed tomography, magnetic resonance imaging or angiography.

Endpoints

Two endpoints were evaluated: 1) a combined endpoint of cardiac related hospital readmissions and cardiac mortality, which is the original primary endpoint of MIND-IT (157), and 2) all-cause mortality. Data concerning date and cause of death was obtained from Statistics Netherlands by linkage to the municipal personal records database. Causes of death with ICD-10 codes I11 (hypertensive heart disease), I20-I25 (ischemic heart diseases), I42-I50 (cardiomyopathy, conduction disorder, cardiac arrest, cardiac dysrhythmia, heart failure) and R57.0 (cardiogenic shock) were considered as cardiac deaths. Data concerning cardiac related readmissions were obtained from the Dutch national registry of hospital discharge diagnosis and were provided by Statistics Netherlands by linkage to the municipal personal records database. Hospital readmissions with the following ICD-9 primary discharge diagnoses were included as cardiac readmissions: ischemic heart disease (410, 411, 413, 414), cardiac arrhythmia (427.1, 427.4, 427.5), heart failure (428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93), cerebrovascular disease (433, 434, 435, 437.0, 437.1) and peripheral vascular disease (440, 443.9).

Data on potential endpoints were gathered up till 31 December 2007. The follow-up period for the endpoints started at the date of randomization, ranging between April 2000 and January 2003. Patients who did not have the outcome of interest until 31 December 2007 were censored on 31 December 2007 or date of death as appropriate.

Statistical analyses

The initial study power calculation showed that 190 patients in the intervention arm and 130 patients in the CAU arm were needed to detect a reduction in the incidence of the primary outcome from 38% to 25% (157). Because the incidence of the primary outcome 18 months post-MI was substantially lower than expected (13% instead of 38% over a mean follow-up period of 11 months (100)),

the study power was recalculated given this event rate, a sample size of 208 and 122 patients in the intervention and CAU arm respectively, an attrition rate of 0.1% per month, an accrual period of 33 months, and a total follow-up period up to 93 months after the MI. This resulted in a study power of 89% and an expected frequency of 67% in the usual care arm versus 49% in the intervention arm for the primary outcome.

With Cox regression, the risk of the endpoints was compared between the intervention and the CAU arms. This was repeated for men and women separately and an interaction effect of treatment status and sex was calculated to evaluate whether the effectiveness of the intervention differed between men and women. Next, with Cox regression the risk of the endpoints was compared between responders and non-responders to antidepressants (response was defined as ≥50% reduction in the HDRS score or a HDRS-score of <10 after 24 weeks of treatment), and between patients who received treatment for depression during the 24-week treatment-period versus those who did not. This analysis excluded patients with no information on whether or not they received treatment for depression as well as patients on placebo in the nested trial. This last group was excluded because of the ambiguity of their treatment status, i.e. they were randomized to the intervention, but received placebo. In case of a statistically significant effect on long-term cardiac outcomes, Chi-square and t-tests were performed to compare baseline characteristics between the groups. Then the analysis was repeated after adjustment for those characteristics that differed significantly between the groups to evaluate whether these may explain the differential risk.

Results

Sample

Figure 1 shows the flow-chart. Baseline characteristics for patients in each randomization arm are described previously (100). Data on the primary outcome of cardiac readmissions and cardiac mortality after randomization were present for 295 patients with a mean follow-up of 4.4 years (standard deviation (SD) 2.4 years: range 2 days – 7.7 years). Analyses with all-cause mortality as endpoint included 330 patients with a mean follow-up of 5.2 years (SD 2.1 years, range 19 days to 7.7 years).

Antidepressant intervention

A previous publication presents details concerning the intervention (100). Briefly, of 209 patients allocated to the intervention group, 13 were lost after randomization and had no information about depression treatment. Forty-five patients received no antidepressant treatment, 17 received open pharmacological treatment with citalopram, 40 received non-pharmacological treatment (i.e. psychotherapy, counseling etc.), and 94 were included in the nested RCT on the efficacy of mirtazapine and/or citalopram. Of the 94 patients in the nested trial, 47 received mirtazapine of whom 27 (57%) responded at week 8, 44 received placebo of whom 18 (41%) responded and 3 did not show up. Non-responders (20+23) were offered open pharmacological treatment (citalopram first choice) (see also **Figure 1**).

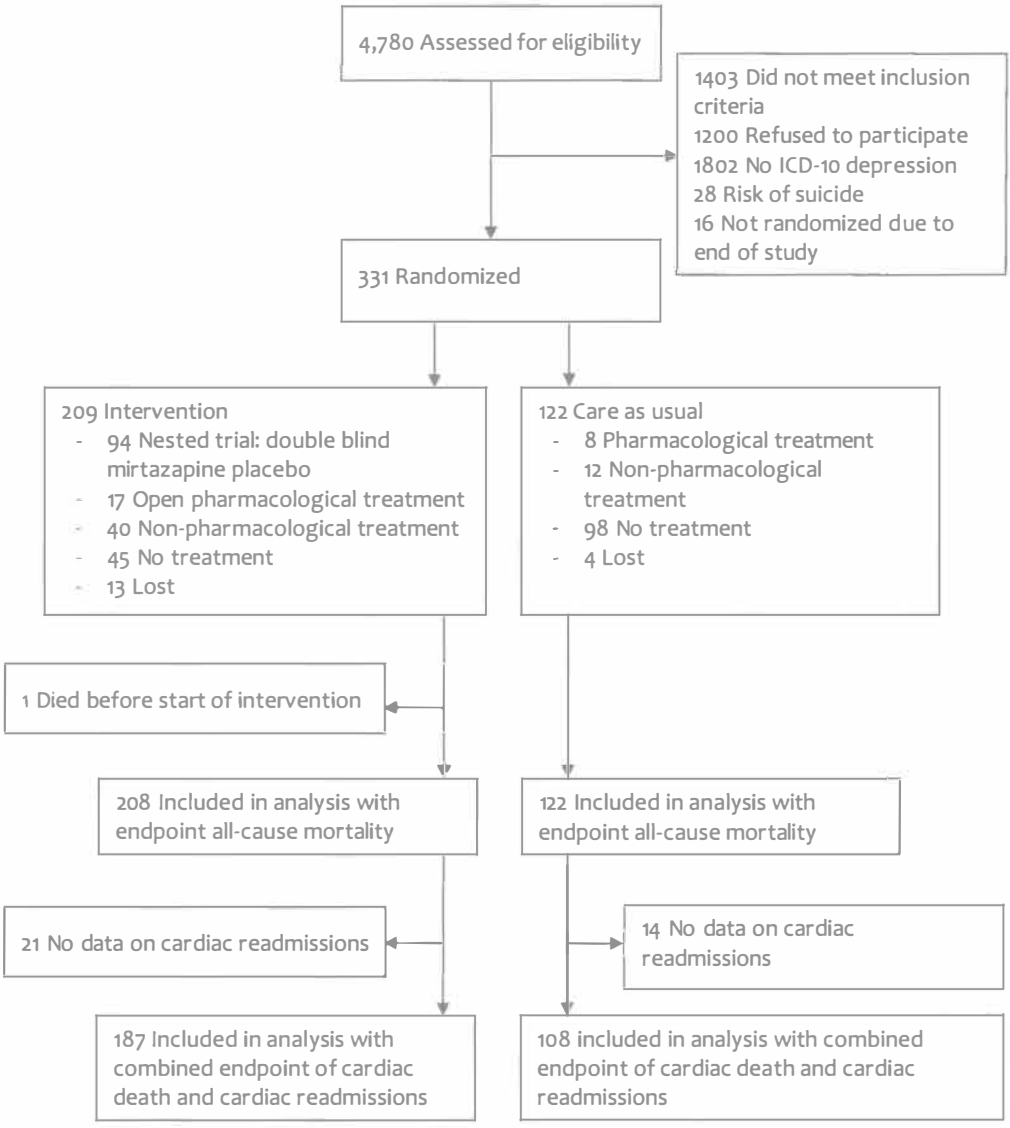

Figure 1. Flow-chart of patients in MIND-IT

Overall effectiveness of the intervention

Of the 295 patients included in analyses with the combined endpoint, 118 (40.0%) had the combined endpoint of cardiac death or cardiac readmission. This was 74 (39.6%) in the intervention arm and 44 (40.7%) in the CAU arm (hazard ratio (HR); 95% confidence interval (CI): 0.96; 0.66-1.39, see **Figure 2** for the Kaplan Meier curve). Of the 330 patients included in analyses with all-cause mortality as an endpoint, 46 (13.9%) died. This was 26 (12.5%) in the intervention arm and 20 (16.4%) in the CAU arm (HR (95% CI): 0.74 (0.41-1.33)).

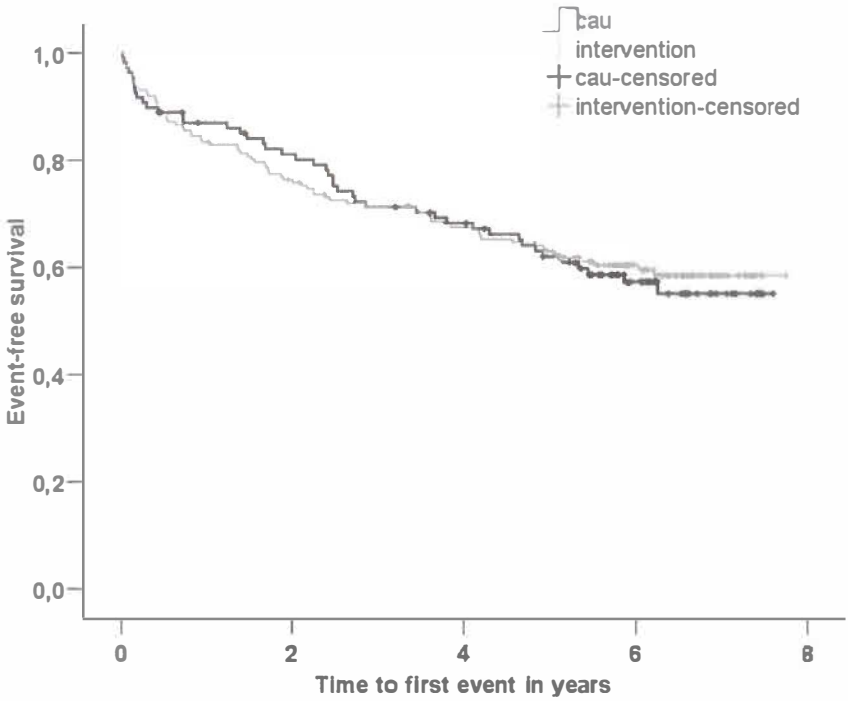

Figure 2. Kaplan Meier survival curve for cardiac related readmissions or cardiac mortality after randomization associated with the intervention or CAU.

Effectiveness of the intervention in men and women

Of 295 patients included in the analyses with the combined endpoint, 218 were men. Of these, 140 were randomized to intervention of whom 55 (39.3%) had the combined endpoint and 78 were randomized to CAU of whom 34 (43.6%) had the combined endpoint (HR (95% CI): 0.88 (0.58-1.35) p=0.568). Of the 77 women, 47 were randomized to the intervention of whom 19 (40.4%) had the combined endpoint and 30 were randomized to CAU of whom 10 (33.3%) had the combined endpoint (HR (95% CI): 1.21 (0.56-2.61) p=0.620).

Of the 330 patients included in analyses evaluating all-cause mortality, 248 were men. Of these, 158 were randomized to the intervention of whom 18 (11.4%) died and 90 were randomized to CAU of whom 13 (14.4%) died (HR (95% CI): 0.77 (0.38-1.58) p=0.772). Of the 82 women, 50 were randomized to the intervention of whom 8 (16.0%) died and 32 were randomized to CAU of whom 7 (21.9%) died (HR (95% CI): 0.71 (0.26-1.95) p=0.503).

The treatment*sex interaction was not significant for the combined endpoint (HR (95% CI): 1.39 (0.58-3.33) p=0.466) nor for all-cause mortality (HR (95% CI): 0.92 (0.27-3.18) p=0.894).

Response to treatment with antidepressants

In the nested trial, 47 patients received mirtazapine and 44 placebo. After 8 weeks, 23 patients in the placebo group switched to citalopram, resulting in a total of 70 patients receiving antidepressants. Of these, there were 27 responders and 43 non-responders at the end of the 6-month treatment period. Twenty-six responders and 38 non-responders had complete data on the combined endpoint, which occurred in 9 (34.6%) of responders and 14 (36.8%) of non-responders (HR (95% CI): 0.98 (0.42-2.25)). Three (11.1%) of the 27 responders died versus 5 (11.6%) of the 43 non-responders (HR (95% CI) for responders: 0.98 (0.23-4.12)).

Treatment versus no treatment for depression

Of 330 patients included in analyses with all-cause mortality, treatment status was unknown for 19 patients and another 21 received placebo only, leaving 290 patients. Of these, 147 received treatment for depression (27 mirtazapine only, 20 initially mirtazapine and later citalopram, 23 initially placebo and later citalopram, 17 open pharmacological treatment, 40 nonpharmacological treatment, 20 of the CAU arm receiving treatment) and 143 did not (45 from the intervention arm and 98 from the CAU arm, see **Figure 1**).

Data on the combined endpoint was present for 130 of 147 patients who received treatment and for 132 of 143 patients who did not. The combined endpoint occurred in 48 (36.9%) of patients who received treatment and in 54 (40.9%) of patients who did not (HR (95% CI): 0.87 (0.59-1.28) p=0.481).

Fourteen (9.5%) of the 147 patients who received treatment died versus 26 (18.2%) of the 143 patients who did not receive treatment (HR (95% CI): 0.52 (0.27-1.00), p=0.049).

Table 1 shows baseline characteristics for the 147 patients who received treatment and the 143 who did not. Patients who received treatment were significantly more likely to be men, more often had coronary artery bypass grafting (CABG) during hospitalization for the index-MI, less often had a previous MI, and had higher BDI-scores. Adjustment for these variables did almost not affect the association between treatment status and all-cause mortality (see **Table 2**).

Table 1. Baseline characteristics for 147 MI patients who received treatment for depression and 143 MI patients who did not

	Received treatment (n=147)	Received no treatment (n=143)
Age mean (SD) (n=290)	57.3 (10.7)	59.0 (11.5)
Male n (%) (n=290)*	117 (79.6)	96 (67.1)
Smoking n (%) (n=290)	79 (53.7)	74 (51.7)
Anterior site MI n (%) (n=290)	47 (32.0)	46 (32.2)
Q-Wave MI n (%) (n=287)	101 (68.7)	90 (64.3)
Ventricular fibrillation at hospitalization n (%) (n=290)	11 (7.5)	20 (14.0)
PTCA during hospitalization n (%) (n=290)	68 (46.3)	72 (50.3)
CABG during hospitalization n (%) (n=290)**	11 (7.5)	1 (0.7)
Trombolysis during hospitalization n (%) (n=288)	59 (40.4)	55 (38.7)
LVEF<45% n (%) (n=266)	58 (43.6)	58 (43.6)
Killip Class>1 n (%) (n=289)	14 (9.5)	21 (14.8)
Previous MI n (%) (n=289)*	15 (10.2)	28 (19.7)
Charlson Comorbidity index >2 n (%) (n=286)	31 (21.4)	42 (29.8)
BMI mean (SD) (n=287)	26.8 (4.1)	26.7 (4.4)
BDI at 3 months mean (SD) (n=183)*	13.5 (6.4)	12.0 (5.4)
Depression severity (n=290)		
Mild n (%)	40 (27.2)	47 (32.9)
Moderate n (%)	70 (47.6)	69 (48.3)
Severe n (%)	37 (25.2)	27 (18.9)

BDI: Beck Depression Inventory; BMI: Body Mass Index; CABG: Coronary Artery Bypass Grafting; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; PTCA: Percutaneous Transluminal Coronary Angioplasty; SD: Standard Deviation

* $p<0.05$, ** $p<0.01$

Discussion

Table 2. Receiving treatment for depression and risk of all-cause mortality after adjustment for co-variables

Adjusted for	HR (95% CI) for all-cause mortality associated with treatment
Unadjusted	0.52 (0.27-1.00)*
Sex	0.54 (0.28-1.04)
CABG	0.53 (0.27-1.03)
Previous MI	0.58 (0.30-1.13)
BDI	0.48 (0.25-0.93)*
All above	0.57 (0.28-1.14)

*p<0.05

The present article reports the risk of cardiac events, cardiac mortality and all-cause mortality up till 8 years after treatment initiation for depressed MI-patients enrolled in MIND-IT. MIND-IT aimed to reduce the risk of cardiac events and mortality in depressed MI-patients by implementing an active antidepressant treatment strategy including pharmacological and non-pharmacological treatment. A previous analysis from MIND-IT shows that the intervention had no effect on depression nor on cardiac outcomes up till 18 months after the MI (100). Therefore it is not surprising that the intervention neither affected the risk of long-term cardiac outcomes. In addition, the intervention had no differential effect on long-term cardiac outcomes in men and women, nor did responders to antidepressants differ from non-responders on long-term cardiac outcomes. Receiving antidepressant treatment was associated with reduced all-cause mortality rates, but not with new cardiac events or cardiac mortality.

Consistent with the present study, two previous RCT's found no reductions in all-cause mortality rates for depressed MI- and unstable angina patients randomized to an intervention to treat depression. In the Enhancing Recovery in Coronary Heart Disease trial (ENRICHD), in 2,481 MI-patients with depression or low social support, those randomized to cognitive behavioral therapy (CBT) had no reduced risk of death or non-fatal MI the 4 years following MI compared to those randomized to CAU (99). In the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), in 369 depressed ACS-patients, there was no difference in all-cause mortality during the 8 years following

treatment initiation between patients randomized to sertraline and those randomized to placebo (155).

Two main reasons could explain why MIND-IT's intervention did not improve cardiac outcomes in depressed MI- and unstable angina patients. The first is that the intervention did not affect depression itself (100). The second is the relative good quality of CAU in the Netherlands. Even though patients received no feedback about their depression status, a substantial number of patients in the CAU arm actually received some form of treatment for depression. A more general explanation why treatment for depression in MI-patients does not reduce the risk of poor cardiac outcomes could be that these do not target factors that underlie the association between depression and poor cardiac outcomes, such as cardiac disease severity, poor physical health, non-adherence to cardiac aftercare and rehabilitation programs, decreased physical activity and smoking.

There was no difference between men and women in the effect of the intervention on cardiac outcomes: the intervention did not affect the outcomes in both genders. This is inconsistent with findings from two previous RCT's. The Montreal Heart Attack Readjustment Trial randomized 1,376 MI-patients to CAU or a distress-reducing intervention program involving psychological distress screening and a home nursing intervention during one year. In men, the intervention had no impact on all-cause and cardiac mortality, but in women the intervention tended to increase this risk (152). In ENRICHD, CBT tended to be associated with a reduced risk of death or non-fatal MI in men, but an increased risk in women (99). In these two studies the psychosocial treatment of depression may have increased psychological distress in women by reminding them of their mood problems and thereby inducing adverse health effects. In MIND-IT a substantial part of the patients was treated with antidepressants, which may explain why in MIND-IT the intervention was not associated with poor cardiac outcomes in women.

Response to treatment with antidepressants was not associated with better long-term cardiac outcomes. Previously, a reduced risk of new cardiac events up till 18 months after the index-MI was reported for responders in the same sample (161). In ENRICHD, depression improvements were associated with reduced all-cause mortality rates in patients receiving CBT, but not in patients

receiving CAU (154). In SADHART, depression improvements were associated with reduced all-cause mortality rates in patients receiving both sertraline and placebo (155). A potential reason why the present study could not replicate these findings is that the size of the subgroup was smaller.

Decreased all-cause mortality rates were found for patients who received treatment for depression compared to those who did not. This finding is comparable to a finding from ENRICHD. In ENRICHD, patients in the intervention arm with severe depressive symptoms and those not responding to CBT were offered additional treatment with antidepressants. An additional group in the intervention arm and some patients in the CAU arm were on antidepressants outside the study protocol. In total, 20.6% of patients in the CAU arm and 28.0% of the patients in the intervention arm received antidepressants by the end of the study. While the intervention (CBT) did not reduce the risk of poor cardiac outcomes, antidepressant use was associated with a significantly reduced risk of death or nonfatal recurrent MI (156).

The increased survival for patients receiving treatment for depression may reflect a real treatment response. However, since it represents a non-randomized comparison, the association may also be confounded by factors associated with receiving treatment as well as increased survival. Patients who received treatment were more likely to be men, more often underwent CABG during hospitalization for index-MI, and less often had a previous MI and had higher BDI-scores. Adjustment for these characteristics did not affect the increased survival associated with receiving treatment for depression. Still, one reason why patients who received antidepressant treatment have better survival may be the intrinsic motivation of patients to care for their health. Patients more likely to seek treatment for their depression will probably more likely adhere to cardiac aftercare and live healthier.

Although it remains unclear why patients receiving treatment for depression have better survival, extra attention should be paid to patients not receiving care that is offered to them. Because of its effectiveness design, MIND-IT resembles the clinical situation in the sense that depressed patients were offered treatment, but had also the possibility to refuse treatment. Exactly this aspect made it possible to identify this group of vulnerable patients not receiving treatment that is offered to them. A study by Scherrer et al. also

identified depressed individuals not receiving antidepressant treatment as a group that is at increased risk of poor outcomes. They evaluated the risk of incident MI and all-cause mortality in 93,653 depressed veterans. Of these, 78.7% received antidepressant treatment for at least 12 weeks according to the guidelines. Receiving antidepressant treatment for at least 12 weeks was associated with significantly reduced risks of incident MI and all-cause mortality (162). Because this is an observational finding, it is unclear whether this effect can be attributed to the treatment itself or to factors associated with receiving antidepressant treatment as well as better prognosis, such as the intrinsic motivation of the individuals to care for their health.

It was hoped that treatment for depression would improve cardiac prognosis in depressed MI patients. However, no RCT, including the present, could confirm this to date. The minor effects of the treatment on depression itself could explain why it did not affect cardiac outcomes. From the present study it appears that patients actually receiving the care that is offered to them have better survival than those who do not. What explains this effect remains unclear and should be further investigated. Differences between patients in healthcare seeking behavior may play a role. It is therefore important that depressed MI patients are motivated to follow treatment recommendations, including depression treatment and cardiac aftercare regimens.

Some considerations should be taken into account when interpreting the results of the present study. First, because recruitment of MI-patients took place 10 years ago, our sample may not be representative to the current MI-patient population because in the meantime the medical management of MI has been changed. For example, in MIND-IT less than 50% of the patients underwent PTCA during hospitalization for their index-MI, while this is nowadays the primary procedure for MI. Second, it remains unclear to what extent the results can be generalized to other cardiac patient populations, since MIND-IT included MI-patients only. Third, the prevalence of the primary outcome (40% in the intervention arm and 41% in the CAU arm) was still lower than expected based on the power calculation (49% in the intervention arm and 67% in the CAU arm). The power calculation was based on the event-rate of 13% during the first 11 months of follow-up. After the first 11 months of follow-up, the event-rates have decreased even further, resulting in the lower prevalence of the primary

outcome after 8 years. Therefore, the study power may have been somewhat less than 89%.

Taken together, our results suggest that the implementation of an antidepressant treatment strategy in depressed MI-patients does not affect long-term cardiac outcomes and has no differential effect on long-term cardiac outcomes in men and women or in responders versus non-responders. Although patients receiving treatment for depression had better survival rates, it cannot be confirmed that this is due to the treatment itself.

Chapter 4

Research question: why does treatment for depression not cure the heart?

From the systematic review (151) presented in Chapter 2 it is concluded that screening for depression in cardiovascular care settings will be resource intensive and there is no evidence that it will lead to beneficial outcomes, particularly because of the absence of adequate follow-up treatments for depression. In fact, the six included studies that evaluated the effects of treatment for depression in depressed cardiac patients found treatment for depression to be associated with only modest improvements in depression and no improvements in cardiac outcomes (98-100, 127-129). Chapter 3 presents a re-analysis of one of these trials, MIND-IT, evaluating the effects of treatment for depression on cardiac outcomes using a longer follow-up duration for cardiac outcomes. In this analysis, treatment for depression was still not associated with improvements in the risk of new cardiac events or mortality rates up till 8 years after the treatment initiation in both men and women. Of interest, patients who actually received treatment for depression, regardless of randomization status, had increased survival rates. It remains unclear whether this is due to the treatment itself or to a factor associated with both receiving treatment for depression and survival, such as a healthier lifestyle of the patient.

Taken together, even though depression after MI has consistently been found to be associated with an increased risk of new cardiac events and mortality, treatment for the depression does not improve the cardiac prognosis. In the following chapters, two possible reasons why treatment for depression in MI patients does not improve cardiac prognosis will be evaluated: 1) heterogeneity of post-MI depression, and 2) it is not depression that predicts poor cardiac prognosis in MI patients.

1. Heterogeneity of post-MI depression

One reason why treatment for depression in MI patients does not improve cardiac prognosis may be that depression after MI is heterogeneous. Although the risk of new cardiac events or mortality is higher for depressed than for non-depressed MI patients, not all depressed MI patients will experience a new cardiac event or die earlier. Of the MI patients with depression, some may have a higher risk of new cardiac events or mortality than others. The identification of those MI patients with depression who have the highest risk of new cardiac events and mortality is highly clinically relevant and may help in understanding why depression after MI is associated with poor prognosis. In addition to association with prognosis, some subtypes of depression may also be more resistant to antidepressant treatment than others. There is some evidence for the existence of a subtype of depression that is treatment-resistant and particularly increases risk of worse prognosis. The presence of this subtype of depression may explain why antidepressant treatment does not improve cardiac prognosis. Specifically, linkage between subtypes of depression with the highest cardiovascular risk *and* subtypes of depression with poor treatment response may help to find new ways to prevent the possible cardiotoxic effects of depression.

Treatment-resistant depression and cardiac prognosis

Findings from several studies indicate that treatment-resistant depression after a cardiac event is associated with an increased risk of poor cardiac prognosis (163). The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial found that among 449 depressed MI patients whose depression did not improve after 6 months treatment with cognitive behavioral therapy supplemented with sertraline had increased mortality rates compared to those whose depression did improve during the treatment period (154). A nested sub-trial of the Myocardial Infarction and Depression Intervention Trial (MIND-IT) evaluated in 70 depressed MI patients the effects of the antidepressants mirtazapine and citalopram on depression and risk of new cardiac events. Those patients whose depression did not improve after 6 months treatment with either mirtazapine or

citalopram were at increased risk of new cardiac events compared to those whose depression did improve (161). The Sertraline Antidepressant Heart Attack Trial (SADHART) included 369 depressed acute coronary syndrome patients (i.e. patients hospitalized for MI or unstable angina) and randomized them to 6 months treatment with sertraline or to placebo. In this trial, patients with treatment-resistant depression were at increased risk of all-cause mortality up till 8 years after the treatment initiation, although this increased risk was also found for patients with persisting depression that were treated with placebo (155). Milani et al. evaluated the effects of a cardiac rehabilitation program with exercise training on depressive symptoms and all-cause mortality in 522 coronary heart disease patients. They found patients with persisting or increasing depressive symptoms during the rehabilitation program to have higher all-cause mortality rates than patients with decreasing or constantly low levels of depressive symptoms (164). More recently, they replicated this finding in 151 coronary heart disease patients with additional heart failure (165).

Taken together, in all these studies, heart disease patients whose depression improved during the treatment period had better cardiac prognosis than those with treatment-resistant depression. Patients with treatment-resistant depression therefore represent an extremely high-risk subgroup of depressed cardiac patients. One potential reason for the high risk in this subgroup is that treatment-resistant depression is a reflection of a more severe heart disease and therefore is associated with worse cardiac prognosis. Another potential reason is that this subgroup of patients is non-adherent to antidepressant treatment explaining why their depression is treatment-resistant. Patients who are non-adherent to their antidepressant treatments may also less likely be adherent to cardiac aftercare regimens, including modifying lifestyle, adherence to cardiac medications, rehabilitation, and attendance at scheduled follow-up visits, which may in turn explain the worse cardiac prognosis in these patients.

First-ever depression, new onset depression and cardiac prognosis

Several studies evaluated cardiac prognosis in depressed MI patients associated with the recurrence (i.e. first-ever versus recurrent) and timing of onset (i.e. onset before or after the cardiac event) of the depressive episode. Lespérance

et al compared all-cause mortality rates for 15 depressed MI patients with a recurrent depressive episode and 20 depressed MI patients with a first-ever depressive episode. Six (40%) of those with a recurrent depressive episode died versus 2 (10%) of those with a first-ever depressive episode (166). Grace et al studied in 235 acute coronary syndrome patients with depressive symptoms during hospitalization all-cause mortality rates during the 5 years following hospitalization. In contrast to the finding of Lespérance et al, patients who reported no history of depression before hospitalization had higher mortality rates (23.8%) than patients who reported to have been depressed at least once before hospitalization (14.3%) (167). De Jonge et al compared the risk of new cardiac events between depressed MI patients with incident depression (i.e. a first-ever depressive episode with an onset after the MI) and those with non-incident depression (i.e. either a recurrent depressive episode or a depressive episode with an onset before the MI or both). They found in 119 depressed MI patients that only those with incident depression were at increased risk of new cardiac events. Those with non-incident depression had a similar risk of new cardiac events compared to a group of 349 non-depressed MI patients (168). Dickens et al reported in 167 depressed MI patients an increased risk of cardiac mortality in those with new onset depression compared to those with a depressive episode with an onset before the MI (i.e. pre-MI onset depression). The risk of those with pre-MI onset depression was even lower than that in a group of 273 non-depressed patients (169). Similarly, Parker et al reported in 101 depressed acute coronary syndrome patients an increased risk of new cardiac events associated with new onset depression and with incident depression (170). Carney et al found in 920 depressed MI patients those with first-ever depression to be at increased risk of all-cause and cardiovascular mortality compared to those with a recurrent depressive episode (171).

Taken together, there seems to be a tendency for worse cardiac prognosis associated with first-ever depressive episodes and depressive episodes with an onset after the cardiac event. Several potential mechanisms underlying the increased risk for these patients are discussed in the literature. Some argue that patients with first-ever depression have 'vascular depression', which is depression caused by lesions in the small arteries of the brain due to atherosclerosis. Increased atherosclerosis in the brain would probably also indicate increased atherosclerosis in the heart which could explain worse

cardiac prognosis in these patients. Vascular lesions in the brain have been found to be typically present in individuals with late-life depression (172). Therefore it is argued that patients who become depressed for the first time in their lives after their MI may have vascular depression. In line with this, heart disease patients with first-ever depression appear to have more atherosclerosis than those with recurrent depression (173, 174). Another potential reason for the worse cardiac prognosis of patients with first-ever and new onset depression is that these patients may have a more severe underlying heart disease. In the study of de Jonge et al, patients with incident depression had lower left ventricular ejection fraction than those with non-incident depression (168, 175). One other reason for the worse cardiac prognosis in patients with first-ever and new onset depression may be that the depression in these patients is more resistant to antidepressant treatment than in patients with recurrent and pre-MI onset depression. As previously described, patients with treatment-resistant depression have worse cardiac prognosis than those whose depression improves during treatment. Two studies found first-ever depressive episodes to be more treatment-resistant than recurrent depressive episodes (129, 176). One of these also found new onset depressive episodes to be more treatment-resistant than depressive episodes with an onset before the cardiac event (176).

First-ever, new onset depression: a treatment-resistant and cardiotoxic subtype of depression?

Taken together, there may be a subtype of depression that is resistant to antidepressant treatment and particularly cardiotoxic. The existence of this treatment-resistant, cardiotoxic subtype of depression could explain why antidepressant treatments in depressed cardiac patients do not improve cardiac prognosis. This subtype of depression could be first-ever, new onset or incident depression. The first part of the present thesis investigates this hypothesis.

In Chapter 5, it is evaluated whether MI patients whose depression does not improve with antidepressant treatment have poor cardiac prognosis because they have the cardiotoxic subtype of first-ever depression. Chapter 6 is a systematic review of the literature evaluating whether first-ever depressive episodes and depressive episodes with an onset after the MI are more

cardiotoxic than recurrent depressive episodes and depressive episodes with an onset before the MI. Chapter 7 evaluates cardiac prognosis associated with an increase in depressive symptoms just after the MI, and whether this explains the increased risk for MI patients with new onset depression. Chapter 8 evaluates long-term (i.e. up till 10 years after the MI) cardiac prognosis associated with first-ever and new onset depression.

2. It is not depression that predicts poor cardiac prognosis in MI patients

Another reason why antidepressant treatment has not been found to affect cardiac prognosis in depressed MI patients may be that it is not depression that predicts poor cardiac prognosis. First, the prognostic value of depression may not lie in a diagnosis of major depression, which was the inclusion criterion of the trials, but in subthreshold depressive symptoms. Second, the prognostic value of post-MI depression may completely lie in underlying factors, such as the severity of the heart disease, which the antidepressant treatments do not target.

Also MI patients not meeting diagnostic criteria for major depression may have worse prognosis

Generally, studies used two ways of measuring depression in cardiac patients: 1) by assessing depressive symptoms reported by the patient on a questionnaire and 2) by establishing a clinical diagnosis of major depression obtained with a diagnostic interview. A questionnaire assesses the current presence and severity of depressive symptoms, but does not yield a diagnosis of major depression. In our systematic review, we found that in the studies using both a questionnaire and a diagnostic interview to assess depression in MI patients found that only half of the patients scoring above the cut-off score on a questionnaire had a diagnosis of major depression (151). Still, most studies evaluating the impact of 'depression' after MI on cardiac prognosis (22 out of

30) evaluated the prognostic impact of self-reported depressive symptoms on a questionnaire instead of a diagnosis of major depression obtained by a diagnostic interview (63). Therefore, the worse prognosis associated with 'depression' after MI may extend to MI patients with elevated depressive symptoms, but no diagnosis of major depression.

Somatic versus cognitive depressive symptoms and cardiac prognosis

There are several depression questionnaires, each comprising different sets of symptoms. Some include mainly cognitive and affective symptoms of depression, whereas others include also somatic symptoms of depression. The BDI, which is most commonly used to assess depression in MI patients, includes cognitive, affective and somatic symptoms of depression. However, some somatic symptoms on a depression questionnaire, for instance fatigue, overlap with symptoms of the heart disease. It has therefore been argued that depression questionnaires including somatic symptoms, such as the BDI, may not be suitable for assessing depression in heart disease patients (82). However, particularly somatic/affective depressive symptoms on the BDI are associated with worse cardiac prognosis in MI patients, whereas this association is much weaker or even absent for cognitive/affective depressive symptoms (92, 177-179).

Vital exhaustion

A construct closely related to depression is 'vital exhaustion'. Vital exhaustion is measured with the Maastricht Questionnaire evaluating scores on fatigue, irritability and demoralization (180, 181). Elevated scores on vital exhaustion may be present in the absence of major depression and are related to cardiac prognosis in MI patients (182, 183). Therefore, patients scoring high on vital exhaustion, but who do not meet criteria for a diagnosis of major depression may be at increased risk of worse cardiac prognosis.

Thus, worse cardiac prognosis has been found in MI patients with elevated somatic symptoms of depression or symptoms of vital exhaustion, but who do not necessarily have a diagnosis of major depression. By using major depression as an inclusion criterion, the antidepressant treatments trials

included in the systematic review may not have included the group of heart disease patients with the highest risk. In addition, the treatments for depression evaluated in these trials may not have targeted the cardiotoxic somatic depressive symptoms, vital exhaustion or fatigue. Both these reasons could explain why the trials found no improvements in cardiac prognosis associated with treatment for depression.

Depression may reflect symptoms of the heart disease

One reason why depressed MI patients have worse prognosis than non-depressed MI patients is that depression partly reflects symptoms of the heart disease, suggesting that depressed MI patients have a more severe underlying heart disease. Indeed, MI patients with depression often have worse underlying heart disease, such as low left ventricular ejection fraction (58). Adjusting for severity of the underlying heart disease attenuates the strength of the association between depression and cardiac prognosis by 45% (57), suggesting that heart disease severity indeed underlies a substantial part of the association between depression and cardiac prognosis. In a study evaluating the association between elevated depressive symptoms on the BDI, heart disease severity and cardiac prognosis in 288 MI patients, heart disease severity strongly predicted cardiac prognosis, but elevated depressive symptoms did not. A potential reason why depressive symptoms were not associated with cardiac prognosis is that, in contrast to most other studies, depressive symptoms were not associated with heart disease severity in this sample (184). Although the absence of this relationship in this sample remains unclear, it suggests that the association between depressive symptoms and cardiac prognosis found by most studies could be explained by heart disease severity. Another study found in 672 MI patients depressive symptoms on the BDI to be associated with risk of sudden cardiac death. However, the association completely disappeared after statistically adjusting for the presence of fatigue (89). Fatigue after MI may be a result of poor cardiac output due to an injured heart, but is also one of the somatic symptoms of depression. Thus, there appears to be substantial overlap between depressive symptoms and symptoms of the heart disease, and a more severe heart disease may therefore explain the worse cardiac prognosis

associated with depressive symptoms. This could in turn explain why antidepressant treatments evaluated so far do not affect cardiac prognosis.

In Chapter 8, it is evaluated whether depressive symptoms reported by the patient on a questionnaire are a stronger predictor of poor cardiac prognosis than a diagnosis of major depression obtained by a psychiatric interview. In addition, it is evaluated to what extent cardiac disease severity explains the risk of poor cardiac prognosis associated with depressive symptoms. Chapter 9 evaluates the overlap between somatic depression and vital exhaustion in MI patients.

Exploring the association between post-myocardial infarction depression and cardiovascular prognosis

Chapter 5

The effects of treatment-resistant depression and first-ever depression on mortality following acute coronary syndrome: interactive or independent?

Marij Zuidersma, Peter de Jonge

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TO THE EDITOR: Drs. Carney and Freedland (163) presented a fascinating review on treatment-resistant depression and mortality following acute coronary syndrome. As a possible mechanism explaining the association between treatment-resistant depression and mortality in acute coronary syndrome patients, the authors suggested the presence of first-ever depressive episodes, which are associated with both treatment resistance and increased risk of cardiac events.

We therefore explored the association between treatment-resistant depression, first-ever depression, and cardiovascular prognosis using data from the Myocardial INfarction and Depression Intervention Trial (MIND-IT), a multi-center randomized controlled trial on the treatment of post-acute coronary syndrome depression. We previously reported (161), using Cox regression analysis, that patients who did not respond to treatment had an unadjusted hazard ratio of 4.89 (95% confidence interval [CI]=1.08–22.10) for new cardiovascular events relative to patients who responded to treatment. Testing the hypothesis of Drs. Carney and Freedland, we adjusted for the presence of first episodes. However, adjusting hardly affected the association (hazard ratio=4.42; 95% CI=0.97–20.10), which is indicative of no support for the hypothesis. An explanation may be that in our sample first episodes were not associated with new cardiovascular events or treatment-resistance. However, they are associated with both new cardiovascular events (hazard ratio=4.12 [95% CI=0.53–31.77]) and with treatment resistance (odds ratio=2.57 [95% CI=0.82–8.03]). The number of patients in each subgroup and their associated risk of cardiac events are shown in **Table 1**.

Our tentative conclusion is that first depressive episodes and treatment-resistance are two independent risk factors for worse outcomes that do not interact but add up independently. Our results do not support the hypothesis that first depressive episodes would underlie the association between treatment-resistant depression and negative cardiac outcomes. Since cell numbers in our study were very low, however, we feel that caution is warranted and no firm conclusions can yet be determined.

We agree with Drs. Carney and Freedland that treatment-resistant depression is likely a marker of an underlying cardiac risk factor associated with treatment-resistance in patients with coronary heart disease and that

researchers should investigate this factor. One possible risk factor that is often overlooked is treatment nonadherence, which is associated with both depression and cardiac prognosis. Treatment nonadherence is one of the reasons for treatment resistance in depressed patients, and it is likely that a patient who is nonadherent to antidepressant treatment is also nonadherent to cardiac aftercare.

Table 1. Patients in Each Subgroup With New Cardiovascular Events

	Group					
	Subjects Responding to Treatment		Subjects Not Responding to Treatment		Total	
Associated Risk Factor	N	%	N	%	N	%
First episode	2/18	11	10/36	28	12/54	22
Recurrent episode	0/9	0	1/7	14	1/16	6
Total	2/27	7	11/43	26	13/70	19

Chapter 6

Onset and recurrence of depression as predictors of cardiovascular prognosis in depressed ACS-patients:

a systematic review

Marij Zuidersma, Brett D Thombs, Peter de Jonge

Psychotherapy and Psychosomatics. 2011; 80:227-237

Abstract

Background: Depression after Acute Coronary Syndrome (ACS) is associated with worse cardiac outcomes. This systematic review evaluated whether depressed ACS patients are at differential risk depending on the recurrence and timing of onset of depressive episodes.

Methods: MEDLINE, EMBASE, and PsycINFO were searched from inception to 11 April 2009. Additionally, reference lists and recent tables of contents of 34 selected journals were manually searched. Eligible studies evaluated cardiovascular outcomes for subgroups of ACS patients with depression or depressive symptoms according to recurrence or onset.

Results: Six studies were included that reported outcomes for subgroups of ACS patients with first-ever versus recurrent depression. Four of these reported also outcomes for post-ACS onset versus pre-ACS onset depression, and incident versus non-incident depression. Worse outcomes (odds ratio>1.4) were reported for ACS patients with first-ever depression in three of six studies (one study $p<.05$); for patients with post-ACS onset depression in three of four studies (one study $p<.05$; but better outcomes in one study) and for patients with incident depression in two of four studies (no studies $p<.05$).

Conclusions: Although it is still suggested that ACS patients with first and new onset depression are at particular increased risk of worse prognosis, the inconsistent results from the studies included in this systematic review show that there is not consistent evidence to support such statements.

Introduction

Depression after acute coronary syndrome (ACS) is associated with an increased risk of new cardiovascular events or mortality. A meta-analysis including 22 studies found that depressed myocardial infarction (MI) patients were at 2-2.5 times higher risk of new cardiovascular events or mortality than non-depressed MI patients (80).

Recently, research is focusing on different aspects of post-ACS depression that may be especially associated with cardiovascular prognosis, such as depression severity (i.e. the distinction between minor and major depression) (185), depressive symptom profile (92, 186), persistence of the depressive episode after the acute event (187) and treatment-resistance (154).

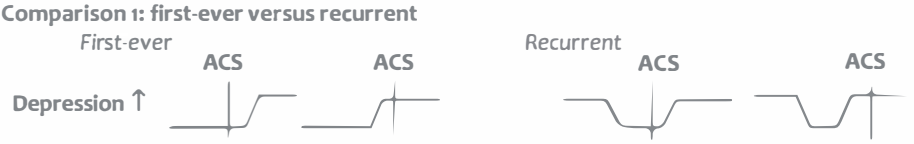
In addition, it has been suggested that the degree to which post-ACS depression is associated with cardiovascular prognosis may be related to the nature and timing of the depressive episode (166-169, 188), including whether the depressive episode is first-ever or recurrent, and whether its onset is before or after the acute event. It was hypothesized that recurrent depressive episodes are associated with worse cardiovascular prognosis than first-ever depressive episodes (166, 167), which was plausible because accumulating exposure to depression may be more harmful than first-ever exposure to depression. The first study that reported data on patients with first versus recurrent depression was published by Lespérance et al. (166) in 1996. In that study, six of 15 MI patients with recurrent depression died by 18 months post-MI (40%) compared to two of 20 MI patients with first episodes during their index hospitalization (10%). A study by Grace et al. (167) almost 10 years later, on the other hand, found depressed ACS patients who reported no history of depressed mood to be at higher risk of mortality five years after the index ACS (31 of 130, 24%) compared to those reporting a history of depressed mood (15 of 105, 14%). In addition to depression recurrence, timing of depression onset (i.e. before or after ACS) has been reported to be related to cardiovascular outcomes. Worse cardiovascular outcomes were reported for patients with post-MI onset or incident (i.e. first-ever and with an onset after the MI) depressive episodes compared to patients with pre-MI onset or non-incident episodes (168, 169).

Post-ACS onset and in particular incident depression may therefore be a distinct subtype of depression with as a unique feature that it may be triggered by the acute event. As a result, this subtype may specifically be associated with worse cardiovascular prognosis.

The objective of the present systematic review was to evaluate whether subgroups of depressed ACS patients are at different risk of subsequent cardiac events or mortality, depending on whether the depressive episode is first or recurrent or whether its onset is before or after the cardiac event. To this end, three subgroup comparisons were examined, depending on whether the post-ACS depressive episode: 1) was first-ever or recurrent, 2) had an onset before or after the cardiac event, or 3) was incident or non-incident (**Box 1**).

Box 1: Subgroups of post-ACS depressed patients, according to recurrence and onset of the depressive episode relative to the acute event

Comparison 1: first-ever versus recurrent



Comparison 2: post-ACS onset versus pre-ACS onset

Comparison 3: Incident versus non-incident

Terminology

First-ever: From the onset of the depressive episode there was no period of feeling better and normal functioning lasting at least 2 months

Post-ACS *onset:* a depressive episode that has an onset after the acute event (i.e. during the acute event the patient was not depressed)

Incident: A depressive episode meeting both of the abovementioned criteria (i.e. first-ever and post-ACS onset)

Methods

Search strategy

MEDLINE, EMBASE and PsycINFO were systematically searched from inception to April 11, 2009. Search strings included appropriate MeSH/EMTREE-terms and free text words for cardiovascular disease, depression and possible cardiovascular outcomes (i.e. 'mortality' and 'event'). In addition, a manual search was done of reference lists from all articles selected for full-text review, relevant reviews, and tables of contents of 34 selected journals from May 1, 2008 to April 11, 2009. Emails were sent to authors of included studies, as well as authors of four key trials (99, 100, 128, 129) on antidepressant treatment in cardiac patients, to query about the possible existence of other published or unpublished eligible studies. Translators were used to evaluate non-English titles/abstracts and articles as necessary.

Study selection

From selected abstracts, all prognostic studies or randomized controlled trials (RCTs) with data on the relationship between post-ACS depression or depressive symptoms and cardiovascular outcomes (i.e. mortality, cardiovascular mortality, recurrent cardiac events) were selected for full-text review. From these, two investigators independently selected papers that were eligible for inclusion. Cohen's Kappa was calculated to assess chance-corrected agreement. Any disagreements were resolved by consensus.

Eligible articles included studies in any language: 1) that were prospective cohort studies or prospective controlled studies (including RCTs); 2) that reported data on patients with ACS (MI and/or unstable angina); 3) that assessed the presence of post-ACS depression with a validated clinical interview (for example the Composite International Diagnostic Interview (CIDI) or the Diagnostic Interview Schedule (DIS)) or depressive symptoms with an established cut-off level on a validated questionnaire (such as the Beck Depression Inventory (BDI) or the 9-item Patient Health Questionnaire (PHQ-9)) within 3 months after the index event; 4) that included cardiovascular

outcomes, defined as all-cause mortality, cardiovascular mortality, or recurrent cardiac events, that occurred after the assessment of post-ACS depression, and were assessed for a period of at least 6 months after the depression assessment; 5) that provided data on outcomes for subgroups of depressed ACS patients with: a) recurrent versus first-ever episodes, b) pre-ACS versus post-ACS onset episodes, and/or c) incident versus non-incident episodes, and 6) that included at least 10 patients with the cardiovascular outcome of interest.

Data-extraction and quality assessment

From the eligible articles, two authors independently extracted information about study cohorts, depression measurement, and outcome measures. Any discrepancies were resolved by consensus. In some cases, data on study characteristics were retrieved from other articles reporting on the same study sample. Some studies reported outcomes for one or two, but not all three subgroup comparisons. If from study methods it appeared that data were available for the missing subgroup comparison(s), authors were asked to provide additional data on the missing subgroups.

For each subgroup comparison in each study an unadjusted odds ratio (OR) with a 95% confidence interval (CI) was calculated to reflect the differential risk of the cardiovascular outcome based on subgroup definitions. Because some studies may be too small to find an increased risk for one subgroup over the other that would reach statistical significance, we did not only consider a statistically significant increased risk, but also "potentially" increased risk as relevant. Because with binary outcomes the magnitude of an OR varies with the prevalence of the outcome, there is no agreed-upon standard for a certain OR to be considered clinically relevant (189). We considered substantive differential risk to be potentially present between subgroups when OR>1.4 or <0.7, regardless of statistical significance. Only unadjusted results were used, because of the small numbers of patients in each subgroup with the outcome (190-192), and because each study used different control variables, which limited the ability to compare multivariable results. The following characteristics were extracted as possible confounders in order to evaluate whether they differed substantively between subgroups: age, gender, left ventricular ejection fraction

(LVEF), Killip Class, history of MI, score on the Beck Depression Inventory (BDI) at baseline, smoking, body mass index (BMI), the presence of diabetes, and use of antidepressants. When these characteristics were not described separately for subgroups in the article, authors were asked to provide them. Whether these characteristics differed significantly between subgroups was evaluated with an independent sample t-test for continuous variables and a chi-square test for dichotomous variables. Because of the small number of included studies, no funnel plot was made to explore possible publication bias.

To assess the quality of the included studies, two investigators independently rated each study on eleven criteria that were generated based on a review by Altman et al. (193). It should be noted that ratings reflect the quality of each study relative to our key questions rather than general quality of the study *per se*.

The search strings, the list of relevant reviews and selected journals that were used with the literature search, the variables that were extracted from the articles, and the quality criteria that were used can be requested from the corresponding author.

Results

Search strategy and selection of articles

The literature search yielded 1,977 unique abstracts. Of these, 104 articles were selected for full-text review. An additional 11 articles were identified for full-text review from manual searching, references of relevant reviews, or references of articles identified for full-text review. Of these, four articles were found to be eligible for inclusion (167, 168, 170, 171), and 111 were excluded (**Figure 1**). Cohen's Kappa for inter-rater agreement was 0.88. In addition, our survey of study authors led to the identification of two more studies meeting all eligibility criteria that were therefore included, as well. The first was an article by Glassman et al. concerning the SADHART study that was in press at the time searches were conducted (155). The second came from an analysis of data of

the MIND-IT study (100), which was presented in a letter to the editor that was in press at the time searches were conducted (194).

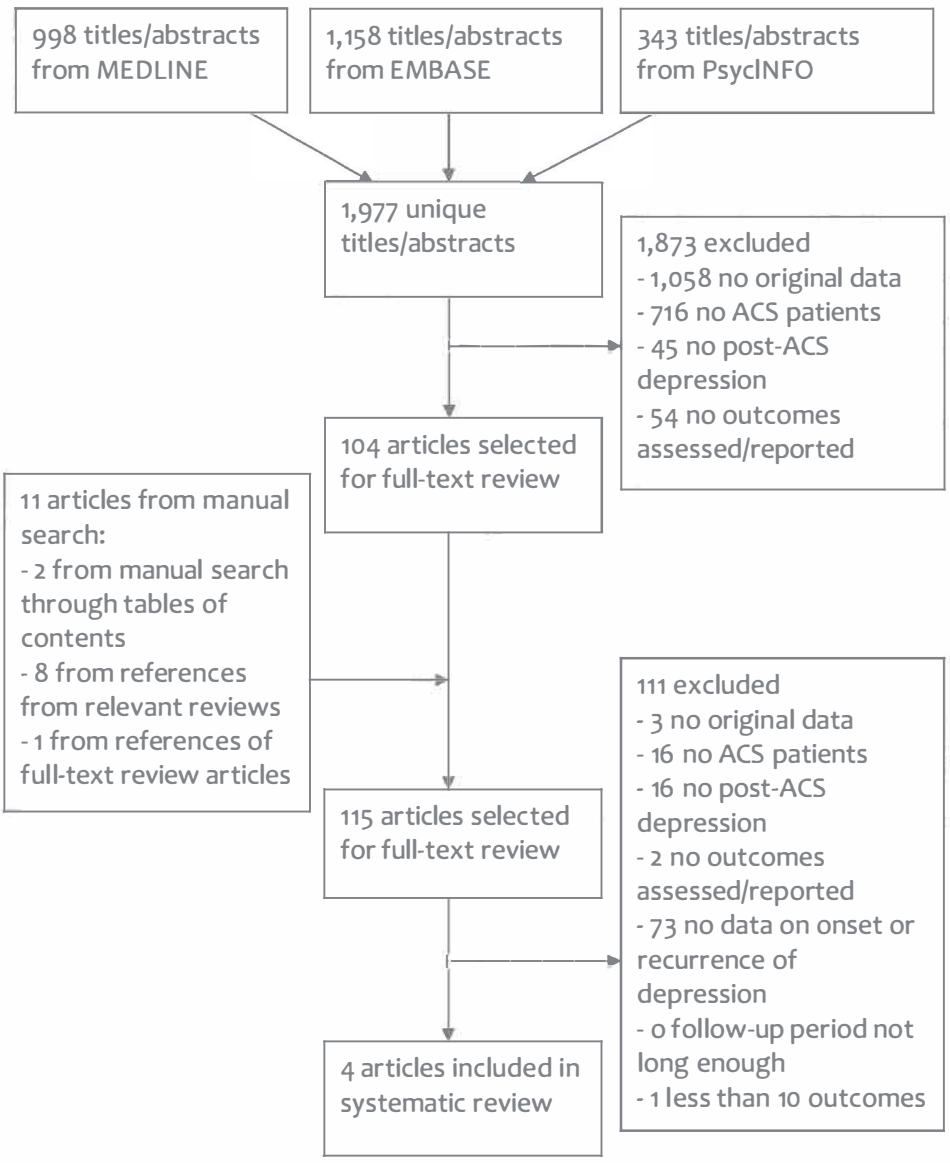


Figure 1: Flow diagram of the search

Retrieval of additional subgroup information on outcomes and baseline characteristics

All six included studies reported outcomes for patients with first versus recurrent depressive episodes. Four of these reported also outcomes for patients with pre-ACS versus post-ACS onset and incident versus nonincident depression. For ENRICHD (171), all information for the subgroups on cardiac outcomes and baseline characteristics could be derived from the article. For the study of Grace et al.(167), the authors provided original data on subgroup characteristics. For SADHART (155) outcomes for patients in all subgroups could be derived from the article, an additional article (176), and additional data on subgroup characteristics were provided by the authors. Parker et al. (170) reported in their article only outcomes for patients with incident, nonincident and post-ACS onset depression. The authors provided original data to also determine outcomes for patients with first, recurrent, and pre-ACS onset depression, as well as data on baseline characteristics for subgroups. De Jonge et al. (168, 195) reported in the original article outcomes for patients with incident versus nonincident depression at 3 or 12 months after the MI. In the present systematic review only patients diagnosed with depression 3 months after the MI were included. Information on outcomes and baseline characteristics for subgroups of patients with first, recurrent, pre-MI onset, post-MI onset, incident and nonincident depression were retrieved from the original data. In this study, the CIDI (196) was used to assess the presence of an ICD-10 post-MI depressive episode. Information about whether the onset of the depressive episode was before or after the MI was obtained by extending the CIDI with additional questions about the presence of each of the depressive symptoms in the four weeks before, and the period after the MI. Outcomes were counted only if they occurred after depression assessment. For MIND-IT, a published letter presented outcomes for patients with first versus recurrent depression in a small subgroup of the MIND-IT sample that received pharmacological treatment for depression (194). In the present systematic review all randomized MI-patients from MIND-IT who were diagnosed with depression 3 months after the MI were included. Information on outcomes and characteristics for all subgroups was retrieved from the original data. As in the de Jonge study (168), information about whether the onset of the depressive episode was before or after the MI was obtained by extending the CIDI with

additional questions. Outcomes were counted only if they occurred after depression assessment.

Study characteristics

Study characteristics and the association of different subgroups with cardiovascular outcomes for the six included studies are shown in **Table 1**. In some cases, study characteristics were retrieved from additional articles about the same sample (100, 128, 176, 195, 197). In the study of Parker et al. (170), all patients with a first episode had incident depression and all patients with nonincident depression had a recurrent episode. This resulted in the same risk estimates for those two subgroup comparisons which is consistent with an overlap of 100% between subgroups. Apart from this example, for the four studies that presented data on multiple subgroup comparisons, the percentage of patients with a given classification that were also classified in another group (e.g., post-ACS onset and incident depression), ranged from 41% to 90%.

Association of subgroups with cardiovascular outcomes and demographical, medical and behavioral characteristics

Table 2 shows the ORs with 95% confidence intervals (CIs) for cardiac outcomes for each of the subgroup comparisons. **Tables 3, 4 and 5** show for each subgroup data on age, sex, LVEF, Killip Class, history of MI, BDI score at hospitalization or within 30 days after the acute event, smoking status, body mass index (BMI), the presence of diabetes mellitus and antidepressant use. The supplemental tables can be requested from the corresponding author.

First-ever versus recurrent depressive episodes

All six studies reported cardiac outcomes for ACS-patients with first-ever versus recurrent depressive episodes. In one of these, patients with a first-ever depressive episode were found to be at significantly increased risk of worse cardiac outcomes (i.e. $p<0.05$). In two of the other studies, patients with first-ever depression were found to be at potentially increased risk (i.e. $OR>1.4$, but $p>0.05$). In the other three studies, no association was found (see **Table 2**). Only

minor differences in baseline characteristics between patients with a first-ever and a recurrent depressive episode that were consistent across studies could be identified: compared to patients with a recurrent depressive episode, patients with a first-ever depressive episode had lower BDI scores, they were somewhat older, and tended less likely to be smokers and to have a history of MI or diabetes (see **Table 3**).

Post-ACS onset versus pre-ACS onset depressive episodes

In four of the six studies cardiac outcomes were reported for ACS-patients with post-ACS onset versus pre-ACS onset depression. In one of these studies patients with post-MI onset depression were found to be at significantly increased risk of worse cardiac outcomes than those with pre-MI onset depression. In two of the others, patients with post-ACS onset depression were found to be at potentially increased risk of worse cardiac outcomes compared to those with pre-ACS onset depression (OR>1.4, p>0.05). In contrast, the fourth study found patients with pre-ACS onset depression to be at potentially increased risk of worse outcomes compared to those with post-ACS onset depression (OR<0.7 for patients with post-ACS onset depression, p>0.05; see **Table 2**). Patients with pre-ACS onset depression tended to have higher BDI scores, tended more likely to have a history of MI, and tended more likely to be on antidepressants, but none of the other baseline characteristics differed consistently across studies between patients with pre-ACS and post-ACS onset depression (see **Table 4**).

Table 1. Study-characteristics and outcomes for studies reporting associations between recurrence and onset of post-ACS depression and cardiovascular prognosis

Authors and Study site	Popula-tion	Definition of post-ACS depression	How and when was depression and its recurrence/onset assessed?	Follow-up period (start-end)	Outcome	Reference group and no (%) of events[2]	Subgroup and no (%) of events	Subgroup and no (%) of events
First versus recurrent							*First*	*Recurrent*
Grace et al. 2005 Canada	750 ACS-patients	Symptoms (BDI>=10)	BDI during hospitalization: history of depression assessed with single question	0-5 years post-ACS	All cause mortality	69/515 (13.4%)	31/130 (23.8%)	15/105 (14.3%)
De Jonge et al. 2006 The Netherlands	442 MI-patients[1]	Current ICD-10 depressive episode	CIDI, 3 mo after MI. + extension to assess onset depression relative to MI	3-54 mo post-MI (mean: 18 mo)	New cardiac events	87/370 (23.5%)	12/52 (23.1%)	4/20 (20.0%)
Parker et al. 2008 Australia	467 ACS-patients	Depressive symptoms on DSM-IV checklist	CIDI within a mean of 3.8 days after ACS + DSM-IV symptom checklist 4 weeks after ACS	1-12 mo post-ACS	Recurrent ACS, cardiac mortality	57/372 (15.3%)	8/25 (32.0%)	12/50 (24.0%)
ENRICHD USA	920 depressed MI-patients	Current episode MDD (DSM-IV)	DISH within 28 days after MI	0-48 mo post-MI (Median duration 29 mo)	1) All-cause mortality 2) Cardio-vascular mortality	1) 14/408 (3.4%) 2) 10/408 (2.5%)	1) 68/370 (18.4%) 2) 41/370 (11.1%)	1) 65/550 (11.8%) 2) 42/550 (7.6%)
SADHART USA, Canada, Europe, Australia	369 depressed ACS-patients	Current episode MDD (DSM-IV)	DIS within 30 days of MI or hospitalization for UA	start within 44 days post-ACS: median duration: 6,7 years	All cause mortality	NA	36/176 (20.5%)	39/183 (21.3%)
MIND-IT The Netherlands	258 depressed MI patients	Current ICD-10 depressive episode+BDI≥10	CIDI 3 months after MI + extension to assess onset depression relative to MI	3 – 18 mo post MI	Cardiac readmissions	Outcomes not assessed	58/206 (28.2%)	15/52 (28.8%)
Post-ACS onset versus pre-ACS onset							*Post-ACS*	*Pre-ACS*
De Jonge et al. 2006 The Netherlands	442 MI-patients[1]	Current ICD-10 depressive episode	CIDI, 3 mo after MI + extension to assess onset depression relative to MI	3-54 mo post-MI (mean: 18 mo)	New cardiac events	87/370 (23.5%)	14/47 (29.8%)	2/25 (8.0%)

Parker et al. 2008 Australia	467 ACS-patients	Depressive symptoms on DSM-IV checklist	CIDI within a mean of 3.8 days after ACS + DSM-IV symptom checklist 4 weeks after ACS	1-12 mo post-ACS	Recurrent ACS, cardiac mortality	57/372 (15.3%)	15/46 (32.6%)	5/29 (17.2%)
SADHART USA, Canada, Europe, Australia	369 depressed ACS-patients	Depressive symptoms on DSM-IV checklist	DIS within 30 days of MI or hospitalization for unstable angina	start within 44 days post-ACS: median duration: 6,7 years	All cause mortality	NA	30/170 (17.6%)	45/189 (23.8%)
MIND-IT The Netherlands	258 depressed MI patients	Current ICD-10 depressive episode+BDI≥10	CIDI 3 mo after MI + extension to assess onset depression relative to MI	3 – 18 mo post MI	Cardiac readmissions	Outcomes not assessed	53/170 (31.2%)	20/88 (22.7%)
Incident versus non-incident							*Incident*	*Non-incident*
De Jonge et al. 2006 The Netherlands	442 MI-patients[1]	Current ICD-10 depressive episode	CIDI, 3 mo after MI + extension to assess onset depression relative to MI	3-54 mo post-MI (mean: 18 mo)	New cardiac events	87/370 (23.5%)	10/33 (30.3%)	6/39 (15.4%)
Parker et al. 2008 Australia	467 ACS-patients	Depressive symptoms on DSM-IV checklist	CIDI within a mean of 3.8 days after ACS + DSM-IV symptom checklist 4 weeks after ACS	1-12 mo post-ACS	Recurrent ACS, cardiac mortality	57/372 (15.3%)	8/25 (32.0%)	12/50 (24.0%)
SADHART USA, Canada, Europe, Australia	369 depressed ACS-patients	Current episode MDD (DSM-IV)	DIS within 30 days of MI or hospitalization for UA	start within 44 days post-ACS: median duration: 6,7 years	All cause mortality	NA	16/90 (17.8%)	59/269 (21.9%)
MIND-IT The Netherlands	258 depressed MI patients	Current ICD-10 depressive episode+BDI≥10	CIDI 3 mo after MI + extension to assess onset depression relative to MI	3 – 18 mo post MI	Cardiac readmissions	Outcomes not assessed	39/130 (30.0%)	34/128 (26.6%)

Abbreviations: ACS = Acute Coronary Syndrome; BDI = Beck Depression Inventory; CI = Confidence Interval; CIDI = Composite International Diagnostic Interview; DIS= Diagnostic Interview Schedule; DISH = Depression Interview and Structured Hamilton; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICD-10 = International Classification of Diseases-10; MDD = Major Depressive Disorder; MI = Myocardial Infarction; NA = Not Applicable; OR = Odds Ratio

[1] For de Jonge et al, 442 patients were included instead of the 468 patients mentioned in their article. The 26 patients that were excluded from the present analysis were only interviewed at 12 months postMI and not at 3 months postMI.

[2] reference group for Grace et al. were patients with BDI<10, for ENRICHD patients with no current MDD episode assessed with DISH + BDI<10, + no previous MDD, for de Jonge et al. no post-MI ICD-10 depressive episode on CIDI at the assessment at 3 months after the MI, for Parker et al: no depression according to DSM-IV checklist 4 weeks after ACS, for SADHART and MIND-IT there was no reference group

Table 2. Odds ratio's for cardiovascular outcomes for the different subgroup comparisons

Author (n with outcome assessed)	*OR (95% CI) for first versus recurrent*	*OR (95% CI) for post-ACS versus pre-ACS onset*	*OR (95% CI) for incident versus non-incident*
Grace et al (n=235)	1.88 (0.95-3.71)[3]	X	X
De Jonge et al. (n=72)	1.20 (0.34-4.28)	4.88 (1.01-23.55)[2]	2.39 (0.76-7.50)[3]
Parker et al (n=75)	1.49 (0.52-4.31)[3]	2.32 (0.74-7.29)[3]	1.49 (0.52-4.31)[3]
ENRICHD (n=920)[1]	1) 1.68 (1.16-2.43)[2] 2) 1.51 (0.96-2.37)[3]	X	X
SADHART (n=359)	0.95 (0.57-1.58)	0.69 (0.41-1.15)[3]	0.77 (0.42-1.42)
MIND-IT (n=258)	0.97 (0.49-1.89)	1.54 (0.85-2.79)[3]	1.19 (0.69-2.04)

Abbreviations: ACS = Acute Coronary Syndrome; CI = Confidence interval; OR = Odds ratio

[1] outcomes evaluated for ENRICHD were 1) all-cause mortality, and 2) cardiovascular mortality (for both outcomes, the number of patients with the outcome assessed was n=920)

[2] Differential risk: significant on the p<0.05 level

[3] Potential differential risk: i.e. OR>1.40 or OR<0.70, but not statistically significant (p>0.05)

Incident versus non-incident depressive episodes

Four of the six included studies reported outcomes for patients with incident versus nonincident depression. Two of these reported a potentially increased risk of worse outcomes for patients with incident depression (OR>1.4, p>0.05). The two other studies found no association between incident versus nonincident depression and cardiac outcomes (see **Table 2**). Patients with nonincident depression tended to have higher BDI scores and tended more likely to have a history of MI, but none of the other baseline characteristics differed consistently across studies between patients with incident and nonincident depression (see **Table 5**).

Table 3. Distribution of demographical, medical and behavioral characteristics between patients with a first-ever and a recurrent depressive episode

		Grace et al. 2005[1] First: 134 Rec: 113	De Jonge et al. 2006[2] First: 52 Rec: 20	Parker et al 2008[3] First: 25 Rec: 50	ENRICHD[4] First: 370 Rec: 550	SADHART[5] First: 176 Rec: 183	MIND-IT[6] First: 206 Rec: 52
Age, mean (SD)	First	**62.8 (12.8)**	57.2 (11.0)	**67.3 (12.5)**	60.7 (12.4)	57.5 (11.4)	58.5 (10.7)
	Rec	**57.6 (10.6)**	57.8 (11.9)	**58.0 (12.2)**	58.4 (12.2)	56.9 (10.1)	58.2 (11.2)
Males, n (%)	First	59 (44.0)	35 (67.3)	16 (64.0)	**55.7**	122 (69.3)	158 (76.7)
	Rec	59 (52.2)	15 (75.0)	30 (60.0)	**45.8**	109 (59.6)	37 (71.2)
LVEF<40%,n (%)	First	NA	12 (23.1)	1 (4.0)	27.6	20 (13.8)	74 (39.6)
	Rec	NA	3 (15.0)	0 (0.0)	27.5	26 (16.1)	23 (45.1)
Killip Class>=2, n (%)	First	32 (25.2)	12 (23.1)	NA	10.3	9 (5.2)	29 (14.1)
	Rec	18 (16.8)	2 (10.0)	NA	9.8	17 (9.3)	8 (15.4)
History MI, n (%)	First	42 (31.3)	5 (9.6)	7 (28.0)	29.1	66 (37.5)	34 (16.5)
	Rec	40 (35.4)	3 (15.0)	19 (38.0)	29.2	85 (46.4)	9 (17.3)
BDI score, mean (SD)	First	**16.1 (6.1)**	11.3 (7.6)	NA	**19.4 (8.2)**	**18.7 (7.0)**	13.2 (7.0)
	Rec	**19.6 (7.3)**	12.4 (7.5)	NA	**22.2 (8.4)**	**22.2 (8.6)**	12.0 (7.0)
Smokers, n (%)	First	43 (32.3)	30 (61.2)	6 (24.0)	**29.2**	43 (24.4)	109 (52.9)
	Rec	49 (44.5)	11 (55.0)	14 (28.6)	**37.5**	58 (31.7)	26 (50.0)
BMI, mean (SD)	First	NA	25.3 (3.6)	NA	**28.4 (5.8)**	29.9 (6.4)	26.5 (4.4)
	Rec	NA	27.4 (4.2)	NA	**29.5 (6.4)**	29.5 (7.0)	26.6 (4.0)
Diabetes, n (%)	First	**78 (59.1)**	4 (7.7)	7 (28.0)	37.4	54 (30.7)	27 (13.1)
	Rec	**85 (80.2)**	3 (15.0)	14 (28.0)	38.2	56 (30.6)	8 (15.4)
Antidepressants n (%)	First	NA	6 (11.5)	1 (4.0)	**5.0**	90 (49.2)	81 (41.5)
	Rec	NA	2 (10.0)	7 (14.0)	**15.5**	96 (51.6)	15 (29.4)

Abbreviations: BDI = Beck Depression Inventory; BMI = Body Mass Index; LVEF = Left ventricular ejection fraction; MI = Myocardial infarction; NA = not available; SD = Standard deviation

Bold: Significant differences; *Italic:* potentially substantive differences, although not significant (when difference in binary variables ≥ 7%, or difference in BDI ≥ 2 points, or difference in BMI ≥ 2 points, or difference in age of ≥ 5 years)

[1] Patient characteristics for Grace et al. are based on 134 patients with first and 113 with recurrent episodes instead of 130 and 105. This is because mortality registry data was not available for 4 and 8 patients in the first and recurrent episodes group, but the specific identity of which patients were missing mortality data was not available. Killip class data were available for 234 patients. Smoking data were available for 243 patients. Diabetes data were available for 238 patients.

[2] For de Jonge et al. information on smoking status was retrieved for 69 of the 72 patients, on BDI for 71 of 72 patients and on BMI for 60 of the 72 patients. Data on antidepressants represent antidepressant use during the 12 months post-MI.

[3] LVEF in study by Parker et al. represents percentage of patients that have LVEF<35%, and antidepressant use represents antidepressant use at discharge

[4] For ENRICHD, for dichotomous variables, only percentages were provided, Killip Class represents percentage of patients with Killip Class III or IV, and antidepressant use represents antidepressant use at baseline

[5] For SADHART LVEF data were available for 306 patients; Killip Class data were available for 356 patients. Data on antidepressants considered all 369 patients with complete data at baseline. The group of patients with antidepressants were the patients randomized to the intervention and the group of patients with no antidepressants were the patients randomized to placebo.

[6] Information on characteristics from MIND-IT concerned 258 of 263 MI patients who were depressed at 3 months (5 missing had no complete baseline data on recurrence and timing of depression). LVEF data were available for 238 patients and represents percentage of patients with LVEF<45%; BDI data were available for 252 patients; BMI data were available for 256 patients, data on antidepressants concerned antidepressant use up till study end (i.e. up till 9-18 months post-MI) and were available for 246 patients, and the number of smokers include also those who stopped smoking < 3 months before event.

Table 4. Distribution of demographical, medical and behavioral characteristics between patients with a post-ACS onset and a pre-ACS onset episode

		De Jonge et al. 2006[1] Post-ACS: 47 Pre-ACS: 25	Parker et al 2008[2] Post-ACS: 46 Pre-ACS: 29	SADHART[3] Post-ACS: 170 Pre-ACS: 189	MIND-IT[4] Post-ACS: 170 Pre-ACS: 88
Age, mean (SD)	Post-ACS	58.5 (11.6)	60.0 (13.6)	56.8 (10.8)	57.9 (11.0)
	Pre-ACS	55.2 (10.2)	62.8 (12.1)	57.6 (10.8)	59.5 (10.5)
Males, n (%)	Post-ACS	32 (68.1)	29 (63.0)	111 (65.3)	126 (74.1)
	Pre-ACS	18 (72.0)	17 (58.6)	120 (63.5)	69 (78.4)
LVEF<40%,n (%)	Post-ACS	10 (21.3)	1 (2.2)	21 (15.3)	67 (41.4)
	Pre-ACS	5 (20.0)	0 (0)	25 (14.8)	30 (39.5)
Killip Class>=2, n (%)	Post-ACS	9 (19.1)	NA	11 (6.5)	26 (15.3)
	Pre-ACS	5 (20.0)	NA	15 (8.0)	11 (12.5)
History MI, n (%)	Post-ACS	4 (8.5)	14 (30.4)	70 (41.2)	**22 (12.9)**
	Pre-ACS	4 (16.0)	12 (41.4)	81 (42.9)	**21 (23.9)**
BDI score, mean (SD)	Post-ACS	10.5 (6.5)	NA	19.9 (8.1)	**12.3 (6.8)**
	Pre-ACS	13.7 (8.8)	NA	21.0 (8.0)	**14.2 (7.2)**
Smokers, n (%)	Post-ACS	26 (57.8)	13 (28.9)	46 (27.1)	92 (54.1)
	Pre-ACS	15 (62.5)	7 (24.1)	55 (29.1)	43 (48.9)
BMI, mean (SD)	Post-ACS	26.4 (4.1)	NA	29.9 (6.6)	26.3 (4.3)
	Pre-ACS	24.8 (3.0)	NA	29.5 (6.9)	26.8 (4.3)
Diabetes, n (%)	Post-ACS	4 (8.5)	11 (23.9)	54 (31.8)	23 (13.5)
	Pre-ACS	3 (12.0)	10 (34.5)	56 (29.6)	12 (13.6)
Antidepressants, n (%)	Post-ACS	4 (8.5)	**1 (2.2)**	80 (46.5)	66 (40.5)
	Pre-ACS	4 (16.0)	**7 (24.1)**	106 (53.8)	30 (36.1)

Abbreviations: BDI = Beck Depression Inventory; BMI = Body Mass Index; LVEF = Left ventricular ejection fraction; MI = Myocardial infarction; NA = not available; SD = Standard deviation

Bold: Significant differences; *Italic:* potentially substantive differences, although not significant (when difference in binary variables ≥ 7%, or difference in BDI ≥ 2 points, or difference in BMI ≥ 2 points, or difference in age of ≥ 5 years)

[1] For de Jonge et al. information on smoking status was retrieved for 69 of the 72 patients, on BDI for 71 of 72 patients, and on BMI for 60 of the 72 patients. Data on antidepressants represent antidepressant use during the 12 months post-MI.

[2] LVEF in study by Parker et al represents percentage of patients that have LVEF<35%, and antidepressant use represents antidepressant use at discharge

[3] For SADHART LVEF data were available for 306 patients; Killip Class data were available for 356 patients. Data on antidepressants considered all 369 patients with complete data at baseline. The group of patients with antidepressants were the patients randomized to the intervention and the group of patients with no antidepressants were the patients randomized to placebo.

[4] Information on characteristics from MIND-IT concerned 258 of 263 MI patients who were depressed at 3 months (5 missing had no complete baseline data on recurrence and timing of depression). LVEF data were available for 238 patients and represent percentage of patients with LVEF<45%, BDI data were available for 252 patients, BMI data were available for 256 patients, data on antidepressants concerned antidepressant use up till study end (i.e. up till 9-18 months post-MI) and were available for 246 patients, and smokers include also those who stopped smoking < 3 months before event.

Table 5. Distribution of demographical, medical and behavioral characteristics between patients with a incident and a non-incident depressive episode

		De Jonge et al. 2006[1] *Incident: 33 Non-inc: 39*	*Parker et al. 2008*[2] *Incident: 25 Non-inc: 50*	*SADHART*[3] *Incident: 90 Non-inc: 269*	*MIND-IT*[4] *Incident: 130 Non-inc: 128*
Age, mean (SD)	Incident	57.7 (12.0)	**67.3 (12.5)**	55.6 (11.1)	57.9 (10.9)
	Non-inc	57.0 (10.5)	**58.0 (12.2)**	57.8 (10.6)	59.0 (10.7)
Males, n (%)	Incident	21 (63.6)	16 (64.0)	60 (66.7)	99 (76.2)
	Non-inc	29 (74.4)	30 (60.0)	171 (63.6)	96 (75.0)
LVEF<40%,n (%)	Incident	9 (27.3)	1 (4)	8 (11.4)	51 (41.5)
	Non-inc	6 (15.4)	0 (0)	38 (16.1)	46 (40.0)
Killip Class>=2, n (%)	Incident	8 (24.2)	NA	5 (5.6)	20 (15.4)
	Non-inc	6 (15.4)	NA	21 (7.8)	17 (13.3)
History MI, n (%)	Incident	3 (9.1)	7 (28)	31 (34.4)	16 (12.3)
	Non-inc	5 (12.8)	19 (38)	120 (44.6)	27 (21.1)
BDI score, mean (SD)	Incident	10.6 (6.6)	NA	**18.9 (7.6)**	12.5 (6.9)
	Non-inc	12.5 (8.2)	NA	**21.0 (8.2)**	13.4 (7.1)
Smokers, n (%)	Incident	18 (58.1)	6 (24)	21 (23.3)	73 (56.2)
	Non-inc	23 (60.5)	14 (28.6)	80 (29.7)	62 (48.4)
BMI, mean (SD)	Incident	25.6 (3.7)	NA	30.7 (6.8)	26.2 (4.3)
	Non-inc	26.1 (4.0)	NA	29.4 (6.7)	26.8 (4.2)
Diabetes, n (%)	Incident	3 (9.1)	7 (28.0)	30 (33.3)	15 (11.5)
	Non-inc	4 (10.3)	14 (28.0)	80 (29.7)	20 (15.6)
Antidepressants, n (%)	Incident	4 (12.1)	1 (4.0)	39 (42.4)	54 (43.9)
	Non-inc	4 (10.3)	7 (14.0)	147 (53.1)	42 (34.1%)

Abbreviations: BDI = Beck Depression Inventory; BMI = Body Mass Index; LVEF = Left ventricular ejection fraction; MI = Myocardial infarction; NA = not available; SD = Standard deviation

Bold: Significant differences; *Highlighted:* potentially substantive differences, although not significant (when difference in binary variables ≥ 7%, or difference in BDI ≥ 2 points, or difference in BMI ≥ 2 points, or difference in age of ≥ 5 years)

[1] For de Jonge et al. information on smoking status was retrieved for 69 of the 72 patients, on BDI for 71 of 72 patients, and on BMI for 60 of the 72 patients. Data on antidepressants represent antidepressant use during the 12 months post-MI.

[2] LVEF in study by Parker et al represents percentage of patients that have LVEF<35%, and antidepressant use represents antidepressant use at discharge

[3] For SADHART LVEF data were available for 306 patients, Killip Class data were available for 356 patients. Data on antidepressants considered all 369 patients with complete data at baseline. The group of patients with antidepressants were the patients randomized to the intervention and the group of patients with no antidepressants were the patients randomized to placebo.

[4] Information on characteristics from MIND-IT concerned 258 of 263 MI patients who were depressed at 3 months (5 missing had no complete baseline data on recurrence and timing of depression). LVEF data were available for 238 patients and represent percentage of patients with LVEF<45%, BDI data were available for 252 patients, BMI data were available for 256 patients, data on antidepressants concerned antidepressant use up till study end (i.e. up till 9-18 months post-MI) and were available for 246 patients, and smokers include also those who stopped smoking < 3 months before event.

Quality of studies

An overview of the quality of the included studies can be requested from the corresponding author. Out of the 11 criteria, the number of criteria with good ratings varied between the five and eight for the six included studies. Three of the studies were RCTs, whereas the other three were observational studies. In all studies, well-defined and appropriate inclusion and exclusion criteria were used. For one study it was clear that of at least 70% of eligible patients completed baseline data. For two studies this was less than 70%, and for the three RCTs this was not reported because of the different study design. In all studies, complete follow-up data was present for at least 70% of the patients with complete baseline data. Only one study provided information about nonparticipants. All, except one, were multicenter studies. Two studies had fewer than 25 patients with the outcome, one between 25 and 50 and three more than 50. In three studies patients were recruited from a consecutive series of clinic admissions or appointments. In four studies post-ACS depression was assessed with a clinical interview (two studies used the CIDI, one study the Depression Interview and Structured Hamilton (DISH) and one study the DIS). In all studies the outcomes were assessed thoroughly and reliably, and in at least five studies outcome assessors were blind to subgroup status. There was no differential loss to follow-up in any of the studies (loss to follow-up occurred only in 0% to 4% of the patients).

Discussion

This is the first systematic review evaluating cardiac prognosis for subgroups of depressed ACS patients. Of the 14 total comparisons included in the review, only two reported a statistically significant ($p<.05$) association between recurrence or onset of depression with cardiovascular outcomes. Because of the inconsistent findings from the studies reviewed, at this time no firm conclusion can be drawn about whether or not first-ever, post-ACS onset and incident depression are related to cardiac prognosis.

There are some considerations that need to be taken into account when interpreting these results. The first consideration is that the number of identified studies is only a small proportion of the total number of studies that have evaluated the impact of post-ACS depression on cardiac prognosis. It is not clear to what degree the set of identified studies is representative of all studies that have been conducted on post-ACS depression and cardiac prognosis. The second consideration is that there were substantial differences between the reviewed studies that may have resulted in the inconsistent findings. Differences in assessment of post-ACS depression may have lead to the inclusion of different patient groups. In addition, within the time-frame of 3 months after the acute event studies differed in timing of depression assessment. A meta-analysis (57) found that depression assessed within 2 weeks after the cardiac event was less strongly associated with cardiac prognosis than depression assessed later than 2 weeks after the cardiac event. In the reviewed studies, however, timing of depression assessment did not seem to have affected the results. Most studies assessed recurrence and timing of onset of the depressive episode differently, and all assessed it retrospectively, which is prone to recall bias (198). This potentially affected the reliability of subgroup classification. Three studies assessed all-cause mortality over long follow-up periods whereas the other three evaluated new cardiovascular events over shorter follow-up periods. A meta-analysis (57) showed that the effect of depression on cardiac prognosis is stronger when using cardiovascular mortality as an outcome compared to all-cause mortality, but that the length of follow-up period did not matter in this association. In the reviewed studies the risk of worse prognosis for subgroups of depressed ACS patients did not seem to be affected by the outcome measure or follow-up length. A third consideration is that two of the six studies only evaluated one of the three subgroup comparisons (167, 171). The three subgroup comparisons are not independent of each other due to the high percentage of patients classified in multiple groups (e.g., post-ACS and incident). A fourth consideration is the quality of the included studies. Not all quality criteria were met by all studies. Three of the included studies were RCT's on antidepressant treatment and three were prospective cohort studies. However, in all three RCT's the intervention had no effect on cardiovascular prognosis, so the associations investigated in the present systematic review are not likely to be affected by the intervention. Two

studies had relatively small numbers of patients with the key outcomes, increasing the chance of spurious findings. Although in the reviewed studies follow-up rates from baseline were very high, in at least two studies less than 70% of eligible patients had complete baseline data and in at least two of the six included studies patients were not recruited consecutively. Only one study provided information about nonparticipants, who were more likely to be female, less likely to be married and on average 7 years older than participants (167). Findings from the included studies may therefore not apply to all ACS patients. A fifth consideration is that psychological distress in patients with a somatic illness is difficult to assess. In order to diagnose and treat medically ill patients with psychological distress properly it is essential to understand many factors that go beyond DSM-IV, such as the patients' life history, temperament and health-related behaviors (199). This inadequacy in diagnostic assessment has been suggested to be the cause of the often inconsistent results in psychosomatic studies (200), and may have contributed to the inconsistent findings of the studies included in this review.

The inconsistent findings across studies and the inability to draw firm conclusions might lead to the suggestion that there is little reason to continue to investigate the relative association of post-ACS depression subgroups with cardiac prognosis. Alternatively, we would argue that this question merits further investigation. There are important limitations in the existing literature in this area, and the question of whether subgroups of depressed ACS patients have worse cardiac outcomes compared to other subgroups is an important one. It has been argued, for instance, that assessments of depression among patients with heart disease may reflect worse underlying heart disease or comorbid conditions beyond what is effectively quantified through covariate adjustment (201, 202). A better understanding of whether certain subtypes of post-ACS depression are qualitatively different from other subtypes would be helpful to understand the overall relationship between depression and cardiovascular outcomes.

No firm consistent pattern of demographical and clinical differences between subgroups was found. The minor differences that were found are very unlikely to underlie the (potentially) increased risk associated with first-ever, post-ACS onset and incident depression in the reviewed studies (167, 168, 170,

171). Some of the studies adjusted for confounding variables in the originally published reports, and concluded that the increased risk of worse outcome for some subgroups was independent from these characteristics. However, the number of patients in most of these studies was too small to effectively use multivariable methods. Furthermore, adjustment for confounders is often imprecise and incomplete. Associations found in studies are often confounded by unmeasured or poorly measured variables, and sometimes even key cardiac variables are, surprisingly, not found to relate to prognosis (201, 203-205). Therefore, it cannot be ruled out that the differential risk of worse outcome between subgroups found by some of the studies are caused by subgroup-imbalances in some measured or unmeasured patient characteristics, such as a more severe underlying coronary artery disease (CAD) (173, 174) or a deteriorating health status. This may also underlie the increased risk of worse prognosis that is found for cardiac patients with somatic rather than cognitive symptoms of depression (92, 177, 178), and ACS patients with persisting or increasing depressive symptoms and treatment-resistant depression (154, 155, 161, 163, 187). MI patients with persisting depressive symptoms report worse physical health 12 months after the MI (206), supporting that a deteriorating health status may indeed underlie the association with worse prognosis. Some depressed ACS patients may have 'vascular depression': a type of depression caused by vascular damage in the brain due to atherosclerosis (207). Recently, an association was found between depressive symptoms persisting up till 3 months after ACS and cerebrovascular lesions (208). Taken together, there may be confounding between depression, somatic health, and cardiovascular outcomes.

Major depression according to DSM-IV criteria is heterogeneous and associated with other psychological constructs, such as hostility and demoralization (209, 210). Subtypes of depression are proposed to exist that differ in etiology, manifestation and are responsive to different kinds of antidepressant treatment (211). The existence of different subtypes of depression in cardiac patients could explain why some subgroups of depressed cardiac patients have worse prognosis than others. In addition, if these subtypes are responsive to different kinds of antidepressant treatment, this could explain why RCT's on antidepressant treatment in depressed cardiac

patients found in general only modest effects in improving depression and no effects in improving cardiovascular prognosis. The identification of subgroups of depressed cardiac patients with different etiology of the depression and different risk of worse prognosis could therefore help in the development of more individually targeted antidepressant treatments for depressed cardiac patients.

In summary, findings of studies evaluating differential risk of worse cardiac outcomes for subgroups of depressed ACS-patients depending on recurrence and onset of the depressive episode are inconsistent. Major methodological differences between the studies may explain the inconsistencies. It is possible that relationships between these subtypes of post-ACS depression and cardiac outcomes reported by some studies (167, 168, 170, 171) reflect one or more underlying risk factors, such as CAD severity at baseline, a deteriorating health status or 'vascular depression'. These underlying risk factors may also cause the increased risk for patients with persistent and treatment-resistant depression and somatic symptoms of depression found in other studies (92, 154, 155, 161, 177, 178, 187). Identifying high-risk subgroups of depressed ACS patients and possibly underlying risk factors is important for understanding the overall relationship between depression and cardiac prognosis and may potentially lead to the development of more individually targeted interventions.

Acknowledgements

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Chapter 7

An increase in depressive symptoms after myocardial infarction predicts new cardiac events irrespective of depressive symptoms before myocardial infarction

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Abstract

Background: Depression after myocardial infarction (MI) is associated with poor cardiovascular prognosis. There is some evidence that specifically depressive episodes that develop after the acute event are associated with poor cardiovascular prognosis. The aim of the present study was to evaluate whether an increase in the number of depressive symptoms after MI is associated with new cardiac events.

Methods: In 442 depressed and 325 nondepressed MI-patients the CIDI-interview to assess post-MI depression was extended to evaluate the presence of the ICD-10 depressive symptoms just before and after the MI. The effect of an increase in number of depressive symptoms during the year following MI on new cardiac events up till 2.5 years post-MI was assessed with Cox regression analyses.

Results: Each additional increase of one symptom was significantly associated with a 15% increased risk of new cardiac events, and this was stronger for non-depressed than for depressed patients. This association was independent of baseline cardiac disease severity. There was no interaction with the number of depressive symptoms pre-MI.

Conclusions: Our findings suggest that an increase in depressive symptoms after MI irrespective of the state of depression pre-MI that explains why post-MI depression is associated with poor cardiovascular prognosis. Also increases in depressive symptoms after MI resulting in sub-threshold depression should be evaluated as a prognostic marker. Whether potential mechanisms such as cardiac disease severity or inflammation underlie the association remains to be clarified.

Introduction

In myocardial infarction (MI) patients, the prevalence of depressive disorder is about 20% (55), compared to 2% in the general population of comparable age (212). Moreover, depressed MI-patients have a twofold increased risk of poor cardiac prognosis, including all-cause mortality, cardiovascular mortality and new cardiovascular events than those who are not depressed (63).

Recent studies suggest that this risk of poor prognosis differs among subgroups of depressed cardiac patients. At particularly increased risk were those with persistent or treatment-resistant depression (154, 155, 161, 187) somatic depressive symptoms (92, 177, 178), anhedonia (213), and first-ever depressive episodes (167, 171).

There is some evidence that depressed MI patients are at particular increased risk of poor prognosis when the depressive episode has an onset after rather than before the acute event (168-170), but results are inconsistent (155, 214). Moreover, MI-patients with depressive episodes with an onset after the MI were found to have had a more severe MI than those with depressive episodes with an onset before the MI (175).

The finding that the onset of the depressive episode relative to the MI is associated with new cardiovascular events helps in identifying those depressed MI-patients with the highest risk. Furthermore, it suggests that the prognostic impact of post-MI depression has an etiology related to the MI itself. Depression after MI results from either a prolongation of a pre-existing depression or an increase in depressive symptoms after the event, or both. The finding that depressive episodes with an onset after the MI are associated with new cardiovascular events suggests that it is the increase in depressive symptoms after the MI that explains the poor prognosis associated with depression. Therefore, an increase in depressive symptoms after MI could also be associated with poor prognosis if it does not lead to a full diagnosis of depression, or if it occurs on top of a pre-existing depressive episode. No study has yet evaluated whether cardiac prognosis is associated with an increase in depressive symptoms after MI as a continuous measure. In the present study

we evaluate whether an increase in depressive symptoms after MI is associated with poor prognosis in the presence and absence of post-MI depression.

Methods

Description of the studies and participants

The present analysis included depressed and non-depressed MI-patients enrolled in two studies: 1) the Depression after Myocardial Infarction study (DepreMI): a prognostic study evaluating the effects of depression on cardiovascular prognosis in MI patients, and 2) the Myocardial Infarction and Depression Intervention Trial (MIND-IT): a randomized controlled trial (RCT) evaluating the effects of antidepressant treatment in depressed MI patients. Both studies were highly similar in patient recruitment, eligibility criteria, assessment of depression, and participation rates.

DepreMI

DepreMI was a prognostic study evaluating the effects of depression on cardiovascular prognosis in MI patients receiving usual cardiac aftercare. Details of this study have been described previously (195). Patients admitted for MI were recruited from four hospitals in the north of the Netherlands between September 1997 and September 2000. To be included, patients had to have chest pain for at least 20 minutes, increased enzyme levels, and new pathological Q-waves on the electrocardiogram in at least two leads. Excluded were patients with a life expectancy of less than a year due to noncardiac condition, poor physical function, cognitive dysfunction, who were unable to speak or read Dutch, and when follow-up visits were scheduled in a nonparticipating hospital. The study protocol was approved by the ethics committee review board of each of the four participating hospitals.

MIND-IT

MIND-IT was a multicenter randomized controlled trial evaluating the effects of antidepressant treatment in depressed MI patients (for details see (100, 157)). Briefly, patients admitted for MI to one of 11 hospitals in the Netherlands were recruited consecutively between September 1999 and November 2002. To be included, patients had to be ≥18 years of age, and had to have a documented increase in cardiac enzymes together with chest pain during at least 20 minutes or typical electrocardiographic changes. Exclusion criteria were the presence of a disease likely to influence short-time survival, being unable to participate (e.g. not able to communicate or not available for follow-up), already receiving psychiatric care for depression, and participating in another clinical trial. The intervention included prescription of antidepressant medication and/or referral to psychotherapy. The institutional review board at each clinical centre approved the protocol. The treatment was not effective in improving long term depression status (i.e. 18 months post-MI) nor in reducing the risk of new cardiac events (100).

Assessment of demographical and clinical parameters

Demographic and clinical characteristics were assessed during hospital admission for the index MI and from hospital charts. The presence of diabetes mellitus was assessed from the medical charts during hospital stay for the index-MI. Smoking was defined as current smoker or quit smoking less than 3 months before hospital admission. Left ventricular ejection fraction (LVEF) was assessed by echocardiography, radionuclide ventriculography, gated Single Photon Emission Computed Tomography, Magnetic Resonance Imaging, angiography or clinical assessment. In MIND-IT, a modified version (215) of the Charlson Comorbidity Index (216) was calculated as a composite measure of somatic comorbidities.

Assessment of a diagnosis of depression

In DepreMI, at 3 and 12 months after the MI, the presence of a post-MI depressive episode according to *International Classification of Diseases* (ICD)-10 criteria (25) was assessed with the Composite International Diagnostic Interview

(CIDI) (37) version 1.1. In MIND-IT, patients were screened for depressive symptoms with the Beck Depression Inventory (BDI) (158) in the hospital and at 3 months after the MI. Those scoring 10 or higher, were administered the CIDI, version 2.1 at 3 months after the MI to assess whether ICD-10 criteria for a post-MI depressive episode were met. Those with a score below 10 on the BDI and those who did not meet ICD-10 criteria for a post-MI depressive episode were assessed for depression again 3 months later. Assessments for depression were made up till 12 months after the MI.

Change in depressive symptoms after MI

In both studies, the change in depressive symptoms after MI was obtained from the first CIDI interview where the diagnosis of depression was made (i.e. 3, 6, 9 or 12 months after the MI for depressed patients and 3 months after the MI for non-depressed patients). For this goal, the CIDI was extended with additional questions to assess the presence of each ICD-10 symptom of depression during the four weeks before MI and after the MI. Symptoms were graded as either present or absent. A change score was calculated by subtracting the number of depressive symptoms present during the four weeks before the MI from the number of depressive symptoms present after the MI. In MIND-IT, the presence of depressive symptoms just before and after the MI was not assessed in non-depressed patients. Therefore, non-depressed patients were included from DepreMI only.

New cardiac events

New fatal and nonfatal cardiac events occurring after the depression interview were included as endpoints and were assessed by patient interviews, hospital records and data from treating specialists. Endpoints included cardiac deaths and hospital readmissions for recurrent MI, unstable angina, heart failure, and arrhythmia. An independent endpoint committee consisting of at least two cardiologists evaluated whether potential endpoints were cardiac related. The follow-up period started at the date of the interview where the diagnosis for depression was established (i.e. 3, 6, 9 or 12 months post-MI for depressed

patients and 3 months post-MI for non-depressed patients) and lasted up till 18 months (MIND-IT) or 2.5 years after the index-MI (DepreMI).

Statistics

First, demographical and clinical characteristics at the time of the MI were compared between included and excluded study participants with the Chi-square or the independent sample Student t-test. This was repeated for the patients with and without data on new cardiac events.

Next, for the included patients, demographical and clinical characteristics were associated with the continuous measure of the change in number of depressive symptoms after MI with the Mann-Whitney U test and Spearman correlation.

Cox regression was used to assess whether time to first new cardiac event was associated with an increase in depressive symptoms after MI. A hazard ratio (HR) was calculated for new cardiac events associated with each symptom increase. Adjustments for covariables were made stepwise: model 1 adjusted for age and sex, model 2 additionally for LVEF and previous MI because these relate to both depression and cardiac prognosis (58, 217), model 3 additionally for diabetes and smoking because these relate to depression as well as cardiac disease (22, 51, 218), and model 4 additionally adjusted for those cardiac parameters that were associated with an increase in the number of depressive symptoms after MI to explore the possibility that other cardiac disease severity parameters explain the association between an increase in number of depressive symptoms after MI and new cardiac events.

To evaluate whether the presence of somatic comorbidities could explain the association between an increase in depressive symptoms and cardiac events, adjustments were made for the Charlson Comorbidity Index. This was done for MIND-IT patients only, because the Charlson Comorbidity Index was only assessed in MIND-IT. To evaluate whether the occurrence of new cardiac events before depression assessment confounded the association between an increase in depressive symptoms after MI and new cardiac events, 1) adjustment was made for new cardiac events before the interview, and 2) patients with a cardiac event before depression assessment were excluded. This was done for

DepreMI only, because in MIND-IT new cardiac events occurring before the depression assessment were not assessed.

Next, the presence of a dose-response relationship between an increase in depressive symptoms and cardiac events was evaluated. First, it was evaluated whether the risk of having a new cardiac event linearly increases with larger increases in depressive symptoms. For this purpose, the HR for new cardiac events associated with an increase of 1) one or two, 2) three or four, or 3) more than four symptoms increase was calculated, using a decrease or no change in number of symptoms as a reference. Second, it was evaluated whether an increase in depressive symptoms is linearly associated with the number of new cardiac events by calculating a Spearman correlation between the increase in number of depressive symptoms and the total number of cardiac events per follow-up year.

Next, to evaluate whether the association between an increase in number of depressive symptoms after MI and new cardiac events differs between patients with few and many symptoms just before the MI, an interaction term was calculated of the number of depressive symptoms pre-MI and the increase in number of depressive symptoms after MI. With Cox regression the HR for new cardiac events was calculated for the interaction-term with the two main terms in the same model, and in a next step additionally with all covariables included in model 4. A multicollinearity test was done for the number of depressive symptoms pre-MI, the increase in depressive symptoms after MI and the interaction term.

As a sensitivity analysis, the survival analyses were repeated for: 1) depressed and nondepressed patients separately to evaluate whether results differ for patients with and without an ICD-10 diagnosis of post-MI depression, 2) only patients who had a CIDI at 3 months post-MI to evaluate whether results differ due to the timing of assessment of change in depression symptoms after MI. Significance level for all analyses was set at $P < 0.05$ (2-tailed).

Results

Sample

The flow chart is shown in **Figure 1.** Of the 2,705 participants (2,177 from MIND-IT and 528 from DepreMI), 835 (31%) patients had complete data on the change in number of depressive symptoms after MI. Of these 835 patients, new cardiac events were evaluated in 767 (92%) patients of whom 442 met ICD-10 criteria for a post-MI depressive episode. Of these 767 patients, 163 (21.3%) had a new cardiac event during a mean (SD) follow-up time of 1.43 (0.86) years.

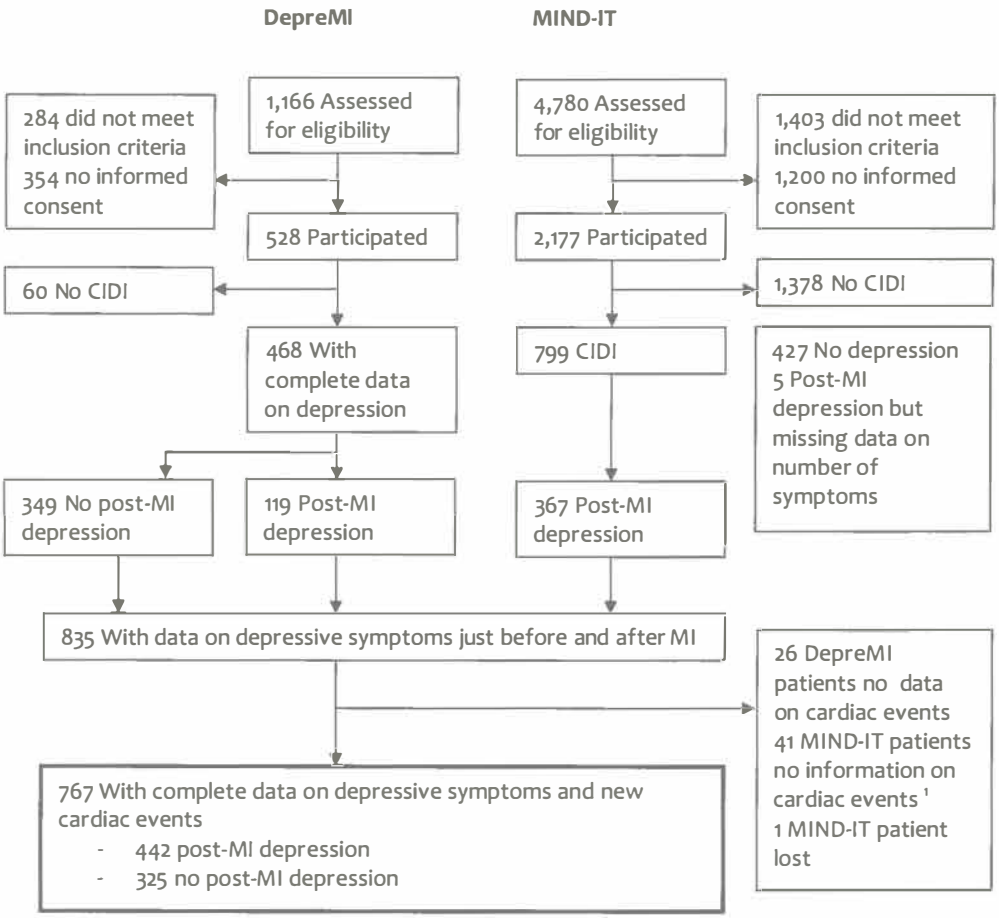

Figure 1. Flow-chart for patients of DepreMI and MIND-IT
[1] These patients were not randomized and therefore not followed for new cardiac events

Characteristics of included and excluded patients

Compared to the 1,938 excluded patients, the 767 who were included in the present analysis were younger, more likely to be smokers, to have lower LVEF, higher Killip Class, to have trombolysis during hospitalization for the index-MI, more likely to be prescribed a calcium channel blocker, less likely to have hypercholesterolemia and less likely to be prescribed statins and beta-blockers. Included and excluded participants did not differ on sex, BMI, smoking, anterior site MI, revascularization during hospitalization for index-MI, history of MI, family history of CAD, diabetes, hypertension, peripheral vascular disease, cerebrovascular disease, and the Charlson comorbidity index (assessed in MIND-IT only).

Compared to the 767 included patients, the 68 with no data on new cardiac events more often had PTCA and less often trombolysis during hospitalization for index-MI. They did not differ on any of the other investigated clinical variables (see above).

Prevalence of depressive symptoms before and after the MI

Table 1 shows for each of the ten ICD-10 symptoms of depression the number of patients and percentages with the symptom before and after the MI. This is done separately for the 442 patients with post-MI depression and the 325 non-depressed patients. It shows that the largest proportion of depressive symptoms after the MI is attributable to new development. However, there seems to be no difference in new development between individual symptoms. In addition, the proportion of patients reporting a symptom to be present before MI but absent after MI was very small, ranging between the 0.8% (appetite problems) and 5.5% (fatigue).

Table 1. Prevalence of each ICD-10 depressive symptom during the 4 weeks before MI and after the MI, assessed in 767 MI patients

	Patients with diagnosis of post-MI depression (n=442)			Patients with no post-MI depression (n=325)		
	Present before MI	Present after MI	Newly developed	Present before MI	Present after MI	Newly developed
Sadness	102 (23.1%)	328 (74.2%)	240 (73.2%)	9 (2.8%)	12 (3.7%)	9 (75.0%)
Loss of interest	81 (18.3%)	278 (62.9%)	214 (77.0%)	12 (3.7%)	19 (5.8%)	13 (68.4%)
Worthless/guilty	44 (10.0%)	176 (39.8%)	143 (81.2%)	6 (1.8%)	13 (4.0%)	8 (61.5%)
Low self esteem	45 (10.2%)	177 (40.0%)	145 (81.9%)	7 (2.2%)	9 (2.8%)	2 (22.2%)
Concentration problems	93 (21.0%)	314 (71.0%)	236 (75.2%)	23 (7.1%)	62 (19.1%)	50 (80.6%)
Thoughts of death/suicide	40(9.0%)	166 (37.6%)	133 (80.1%)	8 (2.5%)	19 (5.8%)	14 (73.7%)
Fatigue	141 (31.9%)	363 (82.1%)	236 (65.0%)	49 (15.1%)	60 (18.5%)	39 (65.0%)
Appetite problems	6 (1.4%)	48 (10.9%)	46 (95.8%)	3 (0.9%)	9 (2.8%)	8 (88.9%)
Sleeping problems	135 (30.5%)	329 (74.4%)	207 (62.9%)	60 (18.5%)	107 (32.9%)	60 (56.1%)
Psychomotor changes	76 (17.2%)	238 (53.8%)	180 (75.6%)	24 (7.4%)	42 (12.9%)	27 (64.3%)

Abbreviations: MI: Myocardial Infarction

Change in number of depressive symptoms after MI and baseline characteristics

Table 2 compares demographical and clinical characteristics for 272 patients with a decrease or no change in depressive symptoms after MI and 495 patients with an increase in depressive symptoms after MI. An increase in number of depressive symptoms was associated with younger age, smoking, low LVEF, anterior site MI, percutaneous transluminal coronary angioplasty (PTCA) during admission for the index-MI, a family history of coronary artery disease (CAD), hypercholesterolemia, and with first-ever depression.

Table 2. Change in the number of depressive symptoms after MI and demographical and clinical characteristics in 767 MI patients

	Decrease or no change in depressive symptoms after MI (n=272)	Increase in depressive symptoms after MI (n=495)	Z (Mann Whitney U test)	Correlation coefficient (r)
Age, mean(SD)	60.7 (11.2)	59.1 (11.5)		-0.101**
Male, n (%)	219 (80.5)	376 (76.0)	-1.476	
BMI, mean (SD)	26.9 (4.2)	26.6 (4.1)		-0.033
Smoking, n (%)	116 (45.8)	266 (56.4)	-2.322*	
Cardiac parameters				
Low LVEF[1], n (%)	71 (26.7)	159 (33.8)	-2.499*	
Anterior site of MI, n (%)	75 (27.6)	179 (36.2)	-2.360*	
Killip Class >=2, n (%)	40 (14.7)	69 (14.0)	-0.375	
PTCA during hospitalization, n (%)	74 (27.7)	185 (38.6)	-4.901***	
CABG during hospitalization, n (%)	15 (5.6)	14 (2.9)	-1.523	
Trombolysis during hospitalization, n (%)	119 (44.2)	207 (42.0)	-1.114	
History MI, n (%)	44 (16.2)	69 (14.0)	-1.005	
Family history of CAD, n (%)	103 (38.0)	226 (46.0)	-3.460**	
Comorbidity				
Diabetes, n (%)	25 (9.2)	61 (12.3)	-0.603	
Hypertension, n (%)	87 (32.0)	151 (30.5)	-0.050	
Hypercholesterolemia, n (%)	113 (41.5)	312 (63.2)	-6.848***	
Peripheral vascular disease, n (%)	18 (6.6)	47 (9.5)	-1.059	
Cerebrovascular disease, n (%)	12 (4.4)	25 (5.1)	-0.419	
First-ever depression[2], n(%)	41 (65.1)	305 (80.5)	-2.831**	

*p<0.05; **p<0.01; ***p<0.001

Abbreviations: BMI: Body Mass Index, CABG: Coronary Artery Bypass Grafting, CAD: Coronary Artery Disease, LVEF: Left Ventricular Ejection Fraction, MI: Myocardial Infarction, PTCA: Percutaneous Transluminal Coronary Angioplasty, SD: Standard Deviation

[1]DepreMI:≤40%, MIND-IT:≤45%

[2]In 442 patients with post-MI depression (n=92 <2 symptoms increase, n=350 ≥2 symptoms increase)

Change in number of depressive symptoms after MI and new cardiac events

Figure 2 shows the mean (95% CI) number of depressive symptoms during the four weeks before MI and after the MI for patients who got a new cardiac event and those who remained event-free. **Table 3** shows the results of the survival analysis. An increase of one depressive symptom was significantly associated with 15% increased risk of new cardiac events. Adjustment for age, sex, LVEF, previous MI, presence of diabetes and smoking did not affect this association. Neither did adjustment for the cardiac parameters that were significantly associated with an increase in depressive symptoms after MI (anterior site MI, PTCA during hospitalization for index MI, family history of CAD, hypercholesterolemia). Adjustment for the Charlson Comorbidity Index in MIND-IT patients did not affect the HR. Adjustment for new cardiac events before the depression assessment affected the HR only slightly (from 1.09 to 1.07), as did exclusion of the 45 patients with a new cardiac event before depression assessment (HR 1.08).

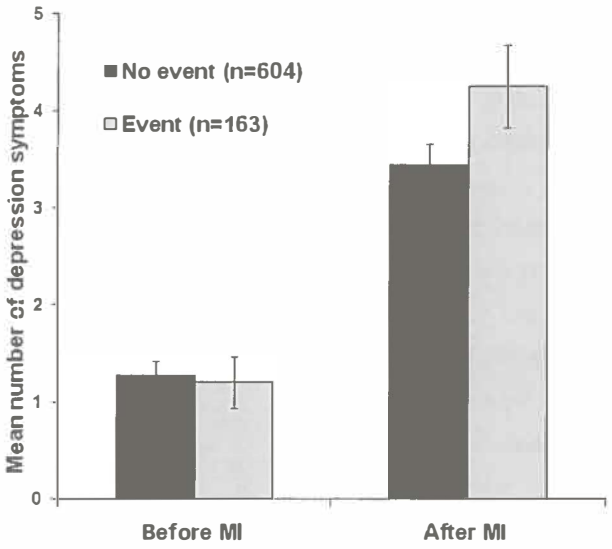

Figure 2. The mean (95% CI) number of symptoms of depression during the four weeks before and after the MI in patients with and without a new cardiac event

There was a dose-response relationship between an increase in depressive symptoms and cardiac events, with unadjusted HR's (95% CI) of 1.70 (1.09-2.66; p=0.020), 2.11 (1.32-3.35; p=0.002), and 2.88 (1.89-4.38; p<0.001) for an increase in one or two, three or four, and more than four symptoms respectively. In addition, the increase in number of depressive symptoms was positively correlated with the number of new cardiac events per follow-up year (ρ = 0.153; p<0.001, see also **Figure 3**).

The interaction term of the number of depressive symptoms pre-MI and the change in number of depressive symptoms after MI did not reach statistical significance. There was no multicollinearity between the number of symptoms pre-MI, the increase in depressive symptoms after MI and the interaction term (Variance Inflating Factor varied between 1.16 and 1.42). The number of symptoms during the four weeks before MI was not associated with new cardiac events. The number of symptoms after the MI was significantly associated with new cardiac events, where each additional symptom accounted for 15% increased risk.

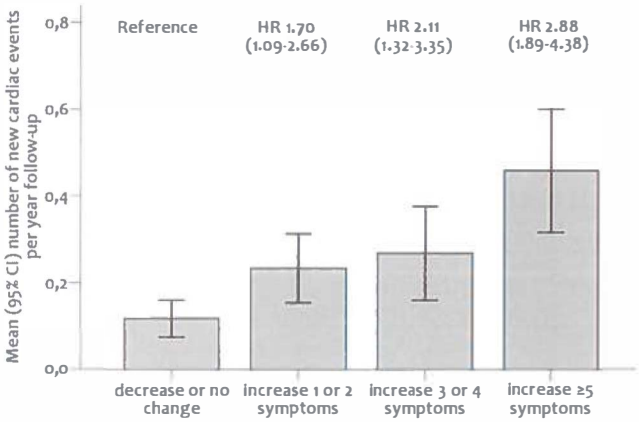

Figure 3. Mean (95% CI) number of new cardiac events per follow-up year and HR (95% CI) for new cardiac events associated with different levels of increase in the number of depressive symptoms just after MI

The first sensitivity analysis shows that in the 442 MI patients with a post-MI depressive episode the association of an increase in number of depressive symptoms after MI and new cardiac events was much weaker than in 325 non-depressed MI-patients (see **Table 3**).

The second sensitivity analysis shows that after exclusion of 134 patients with a CIDI interview at 6, 9 or 12 months, the associations as shown in **Table 3**

were essentially the same (data not described here, but can be requested from the corresponding author).

Table 3. Risk of new cardiovascular events associated with the number of depressive symptoms just before and after MI and with an increase in number of depressive symptoms after MI

	All patients n=767		**Post-MI depression n=442**		**No post-MI depression n=325**	
Predictor	*HR (95% CI)*[1]	*P*	*HR (95% CI)*[1]	*p*	*HR (95% CI)*[1]	*p*
Increase in number of symptoms[2]	1.15 (1.09-1.21)	<0.001	1.08 (1.01-1.16)	0.022	1.21 (1.00-1.46)	0.046
Unadjusted	1.15 (1.09-1.22)	<0.001	1.08 (1.01-1.16)	0.021	1.24 (1.02-1.52)	0.032
Model 1	1.14 (1.08-1.20)	<0.001	1.07 (1.00-1.14)	0.054	1.27 (1.03-1.55)	0.024
Model 2	1.13 (1.07-1.20)	<0.001	1.08 (1.00-1.15)	0.037	1.27 (1.02-1.58)	0.037
Model 3	1.12 (1.06-1.19)	<0.001	1.08 (1.00-1.16)	0.038	1.20 (0.95-1.53)	0.132
Model 4						
Interaction between the number of depressive symptoms pre-MI and increase in number of symptoms after MI[3]	1.00 (0.97-1.03)	0.887	1.01 (0.97-1.04)	0.692	1.14 (0.96-1.36)	0.134
Interaction between the number of depressive symptoms pre-MI and increase in number of symptoms after MI[4]	1.01 (0.98-1.04)	0.719	1.01 (0.98-1.05)	0.546	1.04 (0.89-1.22)	0.613
Number of symptoms pre-MI (unadjusted)	1.00 (0.92-1.08)	0.963	0.91 (0.82-1.00)	0.049	1.12 (0.92-1.35)	0.259
Number of symptoms post-MI (unadjusted)	1.15 (1.09-1.22)	<0.001	1.06 (0.97-1.17)	0.224	1.26 (1.08-1.47)	0.003

[1] HR's indicate the increased risk associated with each additional symptom

[2] Adjusted for: Model 1: age, sex; Model 2: Model 1, LVEF, previous MI; Model 3: Model 2, diabetes, smoking; Model 4: Model 3, anterior site MI, PTCA during hospitalization, family history of CAD, hypercholesterolemia

[3] This model included the number of depressive symptoms pre-MI, the increase in number of depressive symptoms after MI, and the interaction-term of these two

[4] This model included the number of depressive symptoms pre-MI, the increase in number of depressive symptoms after MI, the interaction-term of these two and all variables in model 4

Abbreviations: CAD: Coronary Artery Disease, CI: Confidence Interval, HR: Hazard Ratio, LVEF: Left Ventricular Ejection Fraction, MI: Myocardial infarction, PTCA: Percutaneous Transluminal Coronary Angioplasty

Discussion

In the present analysis we evaluated whether an increase in number of depressive symptoms after MI rather than the prolongation of a pre-existing depressive episode explains why post-MI depression is associated with poor cardiac prognosis. We found a dose-response relation between an increase in number of depressive symptoms after MI and risk of new cardiac events. An increase of one single ICD-10 symptom (of which there are 10) was associated with a 15% increased risk. Although an increase in number of depressive symptoms after MI was associated with cardiac disease severity at baseline, adjustment for cardiac disease severity did not affect the association with new cardiac events. Furthermore, there was no interaction with the number of depressive symptoms pre-MI. This result suggests that it is the increase in depressive symptoms rather than the state of depression pre-MI that explains why post-MI depression is associated with new cardiac events.

Our study has a number of strengths. This is to our knowledge the first time that the impact of an increase in depression severity from just before to after an acute cardiac event on cardiac prognosis is evaluated. We used a large sample of MI patients with and without post-MI depression and assessed the number of depressive symptoms just before and after the MI in a face to face interview. The sample was large enough to adjust for factors potentially confounding the association between the increase in depressive symptoms and new cardiac events. To evaluate to what extent our findings can be generalized to the whole MI population, patients included in the present analysis were compared to excluded participants on baseline demographical and medical characteristics. The oversampling of MI-patients with a diagnosis of depression probably explains why the included patients had a slightly worse cardiac profile than those who were excluded. Apart from this, included patients were not much different from excluded patients. We therefore conclude that the associations we found are very likely to be representative for at least all study participants. In addition, there were no major differences in baseline characteristics between patients with and without data on new cardiac events.

A study that is somewhat comparable to ours is that of Dickens and colleagues (169). In their study, 440 MI patients completed the Hospital Anxiety and Depression Scale (HADS) at two time points: 1) during hospitalization, but assessing depressive symptoms during the week preceding MI, and 2) at 12 months after the MI. They found that patients with new onset depression (i.e. HADS score <17 preceding MI and ≥ 17 at 12 months post-MI) were at increased risk of cardiac mortality up till 8 years post-MI compared to patients with pre-MI onset depression (HADS score ≥ 17 preceding MI) and non-depressed patients (HADS score < 17 at both time points). Despite the difference in assessing the increase in depressive symptoms after MI (i.e. as a continuous measure with a diagnostic interview versus a cut-off score on a questionnaire), our finding is consistent with that of Dickens et al.

It may be that MI patients with depressive episodes with an onset after the MI are at increased risk of new cardiac events (168, 169), because these patients show a larger increase in depressive symptoms after MI. That the increased risk associated with an increase in depressive symptoms after MI is comparable for patients with few and many symptoms of depression pre-MI, suggests that an increase in depression after MI is also associated with poor prognosis 1) in patients with depressive episodes with an onset before the MI, and 2) when it does not lead to a full diagnosis of depression after MI.

The association between the increase in depressive symptoms after MI and new cardiac events suggests that the increase in depressive symptoms as well as the increased risk of new cardiac events have an etiology that is related to the MI, either due to the psychological meaning or the physiological consequences of the event. We found that an increase in depressive symptoms after MI was associated with some cardiac disease severity parameters. This suggests that cardiac disease severity plays a role in the increase in depressive symptoms after MI. However, the association between the increase in depressive symptoms after MI and new cardiac events was independent of cardiac disease severity, suggesting that cardiac disease severity per se does not explain the association. Still, we would not exclude cardiac disease severity as a potential underlying factor. Even though an association is independent of parameters that measure a certain underlying risk factor, the underlying risk factor may still underlie the association, because the parameters are

inaccurately measured or there may be other influential unmeasured parameters (201, 203, 205). For example, like in most prognostic studies on depression and cardiac disease, we measured cardiac disease severity parameters only during hospitalization and made no follow-up assessments. Therefore, we could not evaluate whether an increase in cardiac disease severity explained the poor prognosis in patients with an increase in depressive symptoms after MI. In addition, unmeasured parameters, such as severity of atherosclerosis, could explain the poor prognosis of some patients. Another potential underlying risk factor may be inflammation. Higher levels of inflammatory markers are associated with an increased risk of cardiovascular morbidity, cardiovascular mortality, established cardiac risk factors, among which systolic blood pressure, low-density lipoprotein cholesterol and body mass index (18). In addition, higher levels of inflammatory markers are associated with depression and increased depressive symptoms (36). An increase in depressive symptoms after MI may therefore be associated with an increase in inflammation, which in turn may explain the increased risk of new cardiac events. Whether or not an increase in depressive symptoms after MI is associated with inflammation is yet to be investigated. Still, instead of an underlying physiological process resulting in the increase in depressive symptoms after MI as well as the increased risk of new cardiac events, the increase in depressive symptoms after MI itself may be a precursor of behavioral changes that result in an increased risk of new cardiac events.

The association between an increase in depressive symptoms after MI and new cardiac events was weaker in depressed than in non-depressed MI patients. A possible explanation for this difference is that in depressed MI patients other risk factors, such as medication nonadherence, may overrule the effect of an increase in depressive symptoms after MI. Nevertheless, our finding shows that also in patients who do not meet criteria for post-MI depression, those at increased risk of new cardiac events can be identified. Therefore, also in MI patients with sub threshold levels of depression, it would be useful to assess changes in depression after MI as a prognostic marker for new cardiac events.

Of the patients with post-MI depression, a larger increase in number of depressive symptoms after MI was associated with first-ever depression. There

is some evidence that first-ever depression in MI-patients is associated with poor cardiovascular outcomes (167, 171), but results are inconsistent (155, 214). In the present analysis, first-ever depression was not significantly associated with an increased risk of new cardiac events (HR for new cardiac events: 1.17, 95% CI: 0.73-1.89). Although the results from the present analysis suggest an overlap between first-ever depression and an increase in depressive symptoms after MI, first-ever depression does not seem to explain the increased risk of poor prognosis in patients with an increase in depressive symptoms after MI.

Some considerations should be taken into account when interpreting the findings of the present analysis. One is the retrospective assessment of depressive symptoms just before MI, which may have been subject to recall bias. The presence of previous depressive episodes lifetime is often underestimated, especially by subjects with better current mood (198, 219, 220). In addition, recall of depression just before MI may have been influenced by the MI itself. Therefore, recall bias may have affected the results of the present study. However, for most study participants in the present study the recall period was no more than 4 months and Kendler et al found recall to be significantly better with shorter recall periods (219). Therefore, in the present analysis, underestimation of depression just before MI as well as the effect of current depression severity on this underestimation may well be less prominent. In addition, exclusion of patients who had their depression assessed more than 3 months after the MI did not affect the results, giving a reason to believe that recall bias did not affect the results. Another consideration is that receiving psychiatric treatment at the moment of the index-MI was an exclusion criterion in MIND-IT. This may have lead to the exclusion of patients who were more depressed just before the MI, which could have influenced the results. For DepreMI, scheduled follow-up visit in a non-participating hospital was an exclusion criterion, which lead to the exclusion of 44 patients. This could have introduced some selection bias.

In summary, findings from the present study suggest that an increase in depressive symptoms after MI rather than prolongation of a pre-MI depressive episode explains why post-MI depression is associated with new cardiac events. The increased risk of new cardiac events associated with an increase in depressive symptoms after MI was higher in patients not meeting diagnostic

criteria for post-MI depression than in those with post-MI depression. Therefore, also in patients with sub threshold levels of depression, an increase in depressive symptoms after MI should be assessed as a prognostic marker. Studies should be done to investigate whether potential mechanisms such as cardiac disease severity and inflammation underlie the association.

Chapter 8

Depressive symptoms rather than clinical depression predict cardiac morbidity and mortality following myocardial infarction

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Submitted

Abstract

Context: Despite many years of intensive research, the association between depression and cardiovascular disease is still poorly understood.

Objective: To evaluate the independent prognostic impact of self-reported depressive symptoms and clinical depression assessed with a diagnostic interview on cardiac outcomes during the years following myocardial infarction (MI).

Design, Setting and Patients: 2,704 MI-patients recruited consecutively from 14 hospitals in the Netherlands between September 1997 and November 2002 were administered the Beck Depression Inventory (BDI) and the Composite International Diagnostic Interview at 3 months post-MI.

Main Outcome Measures: All-cause mortality, cardiac mortality and cardiovascular readmissions were evaluated up till 10 years post-MI (mean: 6 years), representing 16,783 persons-years of follow-up. Event-free survival was evaluated using Cox regression analysis.

Results: Analyses on mortality and cardiovascular readmissions included 2,493 and 2,434 patients respectively. There was a strong dose-response relationship between BDI-scores and cardiac outcomes. Compared to patients scoring <5, those scoring ≥19 had age- and sex-adjusted HR's (95% CI) of 3.20 (2.16-4.74, p<0.001) for all-cause mortality, 3.97 (2.06-7.65, p<0.001) for cardiac mortality, and 1.45 (1.08-1.95, p<0.05) for cardiovascular readmissions. Cardiac disease severity and risk factors explained one third to half of this relationship, but the relationship was independent from the presence of clinical depression. Clinical depression on itself was associated with all-cause mortality (HR:1.72 (1.29-2.30, p<0.001)) and cardiac mortality (HR:1.67 (1.01-2.77, p<0.05)) but not with cardiovascular readmissions (HR:1.13 (0.93-1.38, p=0.224)). Adjustment for BDI-scores substantially decreased these HR's towards non-significant. The increased risk associated with BDI-scores was particularly due to somatic/affective symptoms.

Conclusion: After MI, self-reported depressive symptoms on the BDI rather than clinical depression obtained with a diagnostic interview predicted cardiac

morbidity and mortality. This association is mainly due to somatic/affective symptoms of depression and is confounded in a large part by cardiac disease severity.

Introduction

Despite more than 25 years of research on the association between depression and cardiovascular disease, the nature of the association is still poorly understood. Depression after myocardial infarction (MI) is associated with adverse cardiac outcomes (57, 221), but large randomized controlled trials (RCT's) on antidepressant treatment in depressed MI patients found treatment for depression not to improve cardiac outcomes (100, 154).

A major problem of studies in this field is the heterogeneous assessment of depression (222). Most studies evaluating the prognostic impact of depression after MI assessed depression as self-reported depressive symptoms on a questionnaire, while the RCT's on antidepressant treatment included only patients with a diagnosis of clinical depression obtained by a diagnostic interview. There are some major distinctions between the two types of depression assessment. A diagnostic interview evaluates the presence of symptoms of depression that make up a diagnosis of clinical depression according to the diagnostic statistic manual (DSM; (24)) or international classification of diseases (ICD) (25). To be included, each symptom must be present for at least 2 weeks, affect daily functioning and may not be a consequence of a physiological problem. A questionnaire only assesses the current presence and severity of depressive symptoms and some questionnaires also include items that are not DSM symptoms of depression. Because of these differences between a depression questionnaire and a diagnostic interview, a diagnosis of clinical depression and elevated depressive symptoms reported by the patient on a questionnaire may not share the same etiology in MI patients. It is therefore important to distinguish between the

prognostic impact of self-reported depressive symptoms and that of clinical depression and to examine the unique predictive value of each.

Four studies reported the impact on cardiac outcomes of both clinical depression and self-reported depressive symptoms in the same sample. Two found self-reported depressive symptoms to be a stronger predictor for adverse cardiac outcomes than clinical depression assessed with a diagnostic interview in respectively 222 MI patients and 1024 stable coronary heart disease (CHD) patients (67, 101). In contrast, two other studies found clinical depression to be a stronger predictor of adverse cardiac outcomes than self-reported depressive symptoms (117, 223). To date, no study assessed whether the prognostic impact of a diagnosis of clinical depression is independent of the level of self-reported depressive symptoms, and vice versa.

The present study evaluates the independent impact of a diagnosis of clinical depression and self-reported depressive symptoms on new cardiac events and mortality with a mean follow-up of 6 years after the MI in the largest sample of MI patients to date. As secondary analyses, the association of different subtypes of post-MI depression with new cardiac events and mortality were evaluated.

Methods

Patients

Patients were included from the Depression after Myocardial Infarction (DepreMI) study and the Myocardial Infarction and Depression Intervention Trial (MIND-IT). DepreMI is a naturalistic cohort study evaluating the effects of post-MI depression on cardiovascular prognosis in 528 MI patients. Patients admitted for MI were recruited consecutively from four hospitals in the north of the Netherlands between September 1997 and September 2000. MIND-IT is an intervention trial encompassing a total of 2,176 MI patients recruited consecutively from 10 hospitals in the Netherlands between September 1999 and November 2002. Of these, 331 depressed MI-patients participated in the

intervention evaluating the effects of antidepressant treatment. Because the treatment did not affect depression or cardiac outcomes, all patients were included in the present analyses without adjusting for randomization status. Details of these studies have been described before (100, 157, 195). In both studies patients were included if they met at least two of the following criteria for MI: 1) chest pain for at least 20 minutes, 2) typical electrocardiographic changes, and 3) a documented increase in cardiac enzyme levels. Excluded from both studies were patients with another somatic disease likely to influence short-term survival, and patients being unable to participate in study procedures (e.g. were unable to communicate or not available for follow-up). An additional exclusion criterion for MIND-IT was already receiving antidepressant treatment. The institutional review board of each clinical centre approved the protocol of the studies and all participants gave informed consent.

Depressive symptoms and clinical depression

The presence of depressive symptoms was assessed with the Beck Depression Inventory (BDI (158)) during hospitalization and again at approximately 3 months after the MI. The BDI consists of 21 items assessing the presence and severity of depressive symptoms. On each item the score can range from 0 (not present) to 3 (very severe). Consequently, the total BDI-score can range from 0 to 63. Scores of 10 or higher indicate the presence of at least mild depressive symptoms. For the present analysis, BDI-scores were *a priori* categorized based on the BDI manual (40) into scores of 0 to 4, 5 to 9, 10 to 18 and ≥19.

The presence of a post-MI depressive episode according to *International Classification of Diseases* (ICD)-10 criteria (25) was assessed with the Composite International Diagnostic Interview (CIDI (37)) at 3 months after the MI. In DepreMI the CIDI was administered to all patients, in MIND-IT only to those with a BDI-score ≥ 10 at hospitalization and/or 3 months after the MI.

Patients were classified into 3 groups according to the severity of depressive symptoms and a diagnosis of depression: 1) no depression: BDI-score < 10 during hospitalization and at 3 months after MI, 2) depressive symptoms, no clinical depression: BDI-score ≥ 10 at hospitalization and/or 3 months post-MI,

but no diagnosis of a post-MI depressive episode during the first 3 months after MI, and 3) depressive symptoms and clinical depression: BDI-score ≥ 10 at hospitalization and/or 3 months post-MI and a diagnosis of a post-MI depressive episode during the first 3 months after MI.

Recurrence, onset and severity of the depressive episode and depressive symptom profile

We examined differential effects of onset (i.e. before or after the MI), recurrence (i.e. first-ever or recurrent) and severity (i.e. mild, moderate or severe) of the depressive episode, as assessed with the CIDI-interview on cardiac outcomes.

We further examined effects of differential depressive symptom profiles as obtained by the BDI on cardiac outcomes. Therefore, a principal component analysis with oblimin rotation was performed on the BDI. Based on a scree-plot and Eigenvalue>1 the optimal number of factors was set at 3, explaining >42% of the variance. One of the three factors loaded particularly on two items only (loss of appetite and weight loss) and was therefore excluded from the present analysis. The other two factors represented the somatic/affective and cognitive/affective symptoms respectively. Factor scores were calculated on the basis of unstandardized item factor loadings and were z-transformed for interpretation. Details of the factor analysis and factor loadings on each item have been described in detail previously.(92)

Covariates

Age, sex, smoking status and clinical characteristics were assessed during hospitalization for the index-MI and obtained from medical records. Left ventricular ejection fraction (LVEF) was assessed by echocardiography, radionuclide ventriculography, gated single photon emission computed tomography, magnetic resonance imaging or angiography. An adapted version (215) of the Charlson Comorbidity Index (216) was calculated to assess a cumulative burden of somatic comorbidity.

Cardiovascular events and mortality

Data concerning the date and cause of death were derived from Dutch Central Bureau of Statistics by linkage to the municipal personal records database. ICD-10 codes were used to define the cause of death. Deaths with ICD-10 codes I11 (hypertensive heart disease), I20-I25 (ischemic heart diseases), I42-I50 (cardiomyopathy, conduction disorder, cardiac arrest, cardiac dysrhythmia, heart failure) and R57.0 (cardiogenic shock) were considered as cardiac deaths. Data concerning cardiovascular related readmissions came from the Dutch national registry of hospital discharge diagnosis and were provided by the Dutch Central Bureau of Statistics by linkage to the municipal personal records database. ICD-9 codes were used to define the primary hospital discharge diagnoses. Hospital readmissions with the following primary discharge diagnoses were included as cardiovascular readmissions: ischemic heart disease (410, 411, 413, 414), cardiac arrhythmia (427.1, 427.4, 427.5), heart failure (428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93), cerebrovascular disease (433, 434, 435, 437.0, 437.1) and peripheral vascular disease (440, 443.9).

Data on potential endpoints were gathered up till 31 December 2007. The follow-up period for mortality started at the index-MI and for cardiovascular related readmissions at the depression assessment at 3 months post-MI. Patients who did not have the outcome of interest until 31 December 2007 were censored on 31 December 2007 or the date of death as appropriate.

Statistics

Multiple imputation using Stata 10 was used to impute missing data (224). Ten datasets were created where missing values were replaced by imputed values estimated from the observed values. The outcomes were used for imputation of missing predictor values, which has been shown to give more reliable results (225). Patients with missing values on the outcomes themselves were excluded from analyses, because including these adds noise to the estimates (226, 227). Details concerning the imputation model as well as results on complete cases are obtainable upon request. All statistical analyses were performed on the imputed data and Rubin's rules (224) were used to combine results from the

individual datasets. Demographical and clinical characteristics at baseline, BDI-scores and depression status at 3 months post-MI were compared between patients with and without complete data on outcome variables with logistic regression.

Two main research questions were examined. First, the categorized BDI-scores were associated with demographical and clinical characteristics using multinomial logistic regression and with the time to the first endpoint using Cox regression. The survival analysis included four models. In model 1, adjustments for age and sex were made as there were significant differences in the groups with respect to age and sex. In model 2, additional adjustments were made for those cardiac disease severity parameters that are known to relate to depression and cardiovascular prognosis in cardiac patients: LVEF and previous MI (58, 217). Model 3 additionally adjusted for those cardiac risk factors that are known to relate to depression as well as cardiac disease: smoking and the presence of diabetes mellitus (22, 51, 217, 218). The fourth model adjusted for age, sex and clinical depression to evaluate whether the risk associated with self-reported depressive symptoms can be explained by the presence of clinical depression.

Second, we associated depression status (i.e. BDI<10, BDI≥10 and no clinical depression or BDI≥10 and clinical depression) with demographical and clinical characteristics using multinomial logistic regression and with cardiac outcomes using Cox regression. Models 1, 2 and 3 as previously described were used to adjust for covariates. For the comparison between those with clinical depression and those with no clinical depression, a fourth model adjusted for age, sex and additionally for the continuous BDI-score, to evaluate whether the association between clinical depression and adverse cardiac outcomes can be explained by higher BDI-scores in patients with clinical depression.

Finally, exploratory analyses were done to evaluate the prognostic impact of different subtypes of post-MI depression. With Cox regression cardiac outcomes were associated with recurrence, onset and severity of the depressive episode and with the somatic/affective and cognitive/affective factor scores of the BDI. For the analyses concerning recurrence, onset and severity of the depressive episode, adjustments were made for age and sex only, because the sample size in the subgroups was too small to adjust for more covariates

without creating bias (192). For the analyses concerning the factor scores of the BDI, models 1, 2 and 3 as previously described were used to adjust for covariates. A fourth model additionally adjusted for the score on the other factor.

For all survival analyses the proportional hazards assumption was tested by creating interaction terms of the predictors with the time-variable. All statistical analyses were done with Stata 10. Significance level was set at $p<0.05$, two-tailed.

Results

Sample

Data from 2,704 MI patients were used: 2,176 from MIND-IT and 528 from DepreMI. Thirty-two patients (1.2%) died within the first 3 months after MI and were excluded from analysis. Of the remaining sample, 179 patients (6.7%) had missing data on mortality and cardiovascular readmissions and an additional 59 patients had missing data on cardiovascular readmissions only. Therefore, analyses on mortality included 2,493 patients and analyses on cardiovascular readmissions included 2,434 patients (see **Figure 1** for the flow-chart). Patients with missing data on mortality were more likely to have had a previous MI, hypercholesterolemia, and cerebrovascular disease (CVD), but did not differ from those with mortality-data on age, sex, smoking status, body mass index (BMI), anterior site MI, LVEF, Killip Class, revascularization procedures during hospitalization for index-MI, diabetes, hypertension, peripheral vascular disease (PVD), family history of CAD, Charlson Comorbidity Index, cardiac medication at discharge, BDI-score at 3 months post-MI and depression status.

Of 2,493 patients with complete data on mortality, 407 patients died (16.3%) with a mean follow-up of 6.3 (1.9) years, of whom 156 were cardiac deaths (38.3%). Of 2,434 patients with complete data on cardiovascular

readmissions, 878 patients (36.1%) had at least 1 cardiovascular readmission during a mean (SD) follow-up of 4.6 (2.8) years.

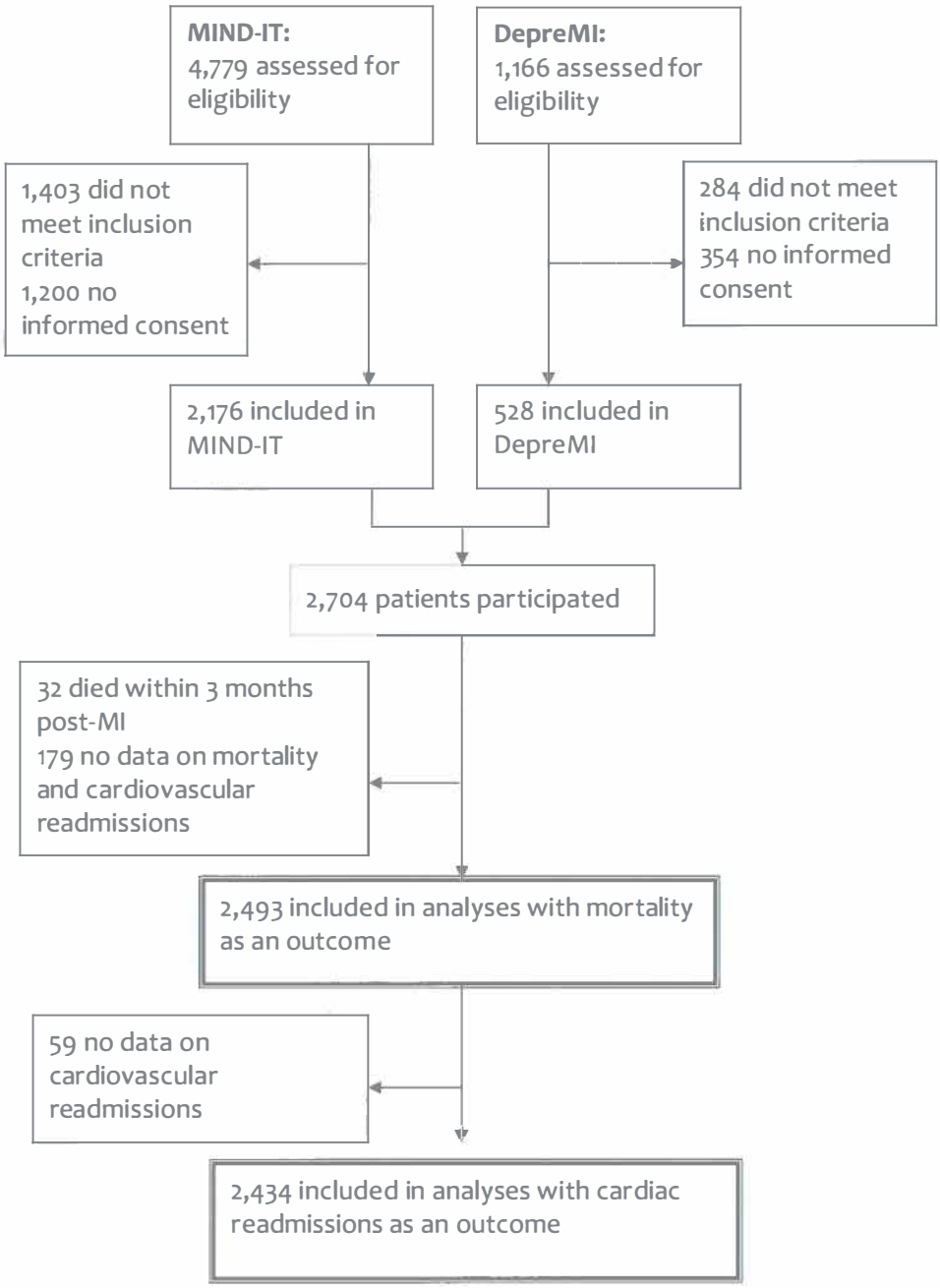

Figure 1. Flow-chart

BDI-scores and baseline characteristics

Of 2,493 patients with complete data on mortality, 1,101 (44.2%) had a BDI-score <5, 759 (30.4%) scored 5 to 9, 480 (19.3%) scored 10 to 18 and 153 (6.1%) scored 19 or higher. Of 2,434 patients with complete data on cardiovascular readmissions, 1,093 (44.9%) had BDI-scores <5, 738 (30.3%) scored 5 to 9, 457 (18.8%) scored 10 to 18 and 146 (6.0%) scored 19 or higher. Higher BDI-scores were associated with female sex, smoking, anterior site MI, low LVEF, higher Killip Class, previous MI, peripheral vascular disease (PVD), cerebrovascular disease (CVD), a higher score on the Charlson Comorbidity Index, more prescription of diuretics, and clinical depression (see **Table 1**).

BDI-scores and cardiac outcomes

Table 2 shows the HR (95% CI) for cardiac outcomes associated with the categorized BDI-scores. There was a dose response association between BDI scores and all-cause and cardiac mortality with increasing risk for patients with higher BDI scores. Adjusting for LVEF and previous MI decreased the risk by 26 to 40%. Additional adjustment for smoking and diabetes decreased the risk with another 2 to 5%. Adjusting for clinical depression did not affect the age- and sex-adjusted risk of all-cause mortality, but *increased* the risk of cardiac mortality with 4 to 16%.

For cardiovascular readmissions, there was no dose-response relationship, but all patients scoring ≥5 on the BDI were at similar increased risk compared to those scoring below 5. Adjusting for LVEF and previous MI attenuated the risk by 10 to 29%. Additional adjustment for smoking and diabetes attenuated this risk by another 0 to 4%. Adjustment for clinical depression *increased* the age-and sex-adjusted risk with 3 to 29%. For all three outcome measures, the proportional hazards assumption was met.

Table 1. Association of BDI-scores at 3 months post-MI with demographical and clinical variables at baseline in 2,493 MI patients

	BDI < 5 (n=1,101)	BDI 5 to 9 (n=759)	BDI 10 to 18 (n=480)	BDI ≥ 19 (n=153)	OR (95% CI) BDI 5-9 vs BDI<5	OR (95% CI) BDI 10-18 vs BDI<5	OR (95% CI) BDI>=19 vs BDI<5
Age, mean (SD)[1]	60.5 (11.3)	61.7 (11.7)	61.5 (12.0)	59.6 (13.1)	1.01 (1.00-1.02)*	1.01 (0.98-1.02)	0.99 (0.98-1.01
Female (%)[1]	18.9	21.7	27.5	29.5	1.20 (0.94-1.52)	1.64 (1.27-2.11)***	1.80 (1.21-2.67)**
Smoker at hospitalization (%)[1]	46.6	48.8	48.6	57.4	1.09 (0.90-1.33)	1.08 (0.87-1.35)	1.55 (1.08-2.22)*
Body mass index, mean (SD)[1]	26.6 (3.6)	26.6 (4.1)	26.5 (4.0)	26.4 (4.3)	1.00 (0.97-1.02)	0.99 (0.96-1.02)	0.99 (0.94-1.04)
Anterior site MI (%)[1]	32.2	34.8	31.2	43.1	1.12 (0.92-1.37)	0.96 (0.75-1.21)	1.60 (1.10-2.32)*
Low LVEF (%)[3]	20.5	25.2	32.6	33.8	1.31 (1.04-1.64)*	1.88 (1.45-2.43)***	1.98 (1.34-2.93)***
Killip Class ≥ (%)[1]	9.8	10.4	14.2	19.2	1.07 (0.77-1.48)	1.53 (1.09-2.16)*	2.19 (1.32-3.65)**
Previous MI (%)[1]	10.2	14.6	16.9	16.7	1.50 (1.13-1.99)**	1.79 (1.31-2.46)***	1.77 (1.08-2.88)*
PTCA during hospitalization (%)[2]	35.6	36.6	37.3	36.1	1.05 (0.85-1.29)	1.07 (0.85-1.35)	1.02 (0.70-1.50)
CABG during hospitalization (%)[2]	5.6	4.2	3.7	4.0	0.74 (0.46-1.18)	0.65 (0.37-1.14)	0.70 (0.28-1.80)
Diabetes (%)[1]	10.7	11.7	15.3	11.3	1.11 (0.81-1.51)	1.51 (1.09-2.08)*	1.05 (0.57-1.93)
Hypertension (%)[1]	31.8	32.9	33.9	37.6	1.05 (0.86-1.28)	1.10 (0.87-1.38)	1.29 (0.90-1.85)
Hypercholesterolemia (%)[1]	68.7	64.1	70.9	65.5	0.82 (0.67-1.00)*	1.11 (0.87-1.41)	0.87 (0.58-1.28)
Peripheral vascular disease (%)[2]	5.6	8.2	11.2	8.4	1.51 (1.02-2.21)*	2.12 (1.40-3.20)***	1.54 (0.79-3.00)
Cerebrovascular disease (%)[2]	3.8	6.9	6.4	7.8	1.89 (1.23-2.90)**	1.75 (1.07-2.85)*	2.16 (1.08-4.31)*
Family history CAD (%)[1]	43.3	44.2	43.9	42.7	1.04 (0.86-1.25)	1.02 (0.82-1.27)	0.98 (0.67-1.41)
Charlson Comorbidity Index, median (IQR)[2]	0 (0-1)	0 (0-2)	1 (0-2)	1 (0-2)	1.16 (1.06-1.26)**	1.26 (1.15-1.38)***	1.26 (1.09-1.45)**
Medication at discharge (%)[2]							
- Aspirin	86.6	83.8	83.8	82.7	0.80 (0.61-1.04)	0.80 (0.59-1.08)	0.74 (0.46-1.21)
- Beta-blocker	85.7	82.4	82.0	82.1	0.78 (0.60-1.02)	0.76 (0.56-1.02)	0.77 (0.46-1.27)
- Calcium antagonist	16.2	21.1	19.3	22.2	1.38 (1.08-1.76)*	1.23 (0.93-1.64)	1.47 (0.95-2.27)
- Diuretics	12.2	15.6	19.2	19.3	1.34 (1.02-1.76)*	1.72 (1.28-2.31)***	1.73 (1.09-2.74)*
- Ace-inhibitor	39.6	43.1	40.4	45.7	1.16 (0.96-1.40)	1.03 (0.82-1.30)	1.28 (0.87-1.88)
- Statin	72.6	69.1	69.0	64.4	0.84 (0.69-1.04)	0.84 (0.66-1.07)	0.68 (0.46-1.00)
Presence of clinical depression (%)[1]	NA	NA	45.8	70.5	NA	NA	2.70 (1.76-4.14)*** (BDI>18 vs BDI 10-18)

Abbreviations: BDI: Beck Depression Inventory; CABG: Coronary Artery Bypass Graft; CAD: Coronary Artery Disease; CI: Confidence Interval; IQR: Interquartile Range; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; NA: not assessed; OR: Odds Ratio; PTCA: Percutaneous Transluminal Coronary Angioplasty; SD: Standard Deviation

*p<0.05, **p<0.01, ***p<0.001 difference from BDI<5 using multinomial logistic regression

[1] Mean, numbers and percentages represent the overall mean, the mean numbers and mean percentages over the 10 imputed datasets. SD's are calculated taking into account Rubin's rule.

[2] Mean, numbers and percentages are based on complete cases, because these variables were not included in the imputation model. PTCA n=2,382, CABG: n=2,379, peripheral vascular disease: n=2,481, cerebrovascular disease: n=2,478, Charlson Comorbidity Index: n=1,934, aspirin: n=2,441, beta-blocker: n=2,478, calcium antagonist: n=2,441, diuretics: n=2,478, ace-inhibitor: n=2,478, statin: n=2,478. The linear regression was performed on cases with complete data on the covariate.

[3] LVEF<40% in DepreMI and LVEF<45% in MIND-IT

Depression status and baseline characteristics

Of 2,493 patients with complete data on mortality, 1,618 (65.7%) had a BDI-score < 10, 479 (19.2%) had a BDI-score ≥ 10, but no clinical depression, and 396 (15.9%) had a BDI-score ≥ 10 and clinical depression. Of 2,434 patients with complete data on readmissions, 1,604 (65.9%) had a BDI-score < 10, 468 (19.2%) had a BDI-score ≥ 10, but no clinical depression and 362 (14.5%) had a BDI-score ≥ 10 and clinical depression.

Table 3 shows demographical and clinical characteristics according to depression status. Compared to patients with BDI<10, those with BDI≥10 and no clinical depression were older, more likely to be female, had lower LVEF, higher Killip Class, more often had a previous MI, diabetes, PVD, and CVD, had a higher score on the Charlson Comorbidity Index, were more likely to be prescribed a beta-blocker, diuretics and statins at discharge, and had higher BDI scores. Compared to patients with BDI<10, those with BDI≥10 and clinical depression were younger, more likely to be female and smoker, had lower LVEF, higher Killip Class, had more often PTCA during hospitalization for index-MI, had more often hypercholesterolemia and PVD, had a higher score on the Charlson Comorbidity Index, and had higher BDI scores. Of patients with BDI≥10, those with clinical depression were younger, had higher LVEF, more often had PTCA during hospitalization, more often had hypercholesterolemia and a family history of CAD, were prescribed statins more often and had higher BDI scores than those with no clinical depression.

Table 2. HR (95% CI) for cardiac outcomes associated with BDI scores at 3 months post-MI

	BDI 0-4	BDI 5-9	BDI 10-18	BDI≥19
All-cause mortality (n/n with data on mortality)	128/1,101 [1]	133/759 [1]	103/480 [1]	43/153 [1]
adjusted for:	Reference			
-age and sex		1.42 (1.10-1.82)**	2.01 (1.53-2.64)***	3.20 (2.16-4.74)***
- age, sex, LVEF and previous MI		1.31 (1.02-1.68)*	1.66 (1.25-2.20)***	2.56 (1.71-3.82)***
- age, sex, LVEF, previous MI, diabetes and smoking		1.29 (1.00-1.66)*	1.62 (1.22-2.14)**	2.47 (1.64-3.70)***
- age, sex and clinical depression		1.41 (1.10-1.81)**	1.96 (1.46-2.62)***	3.05 (1.98-4.71)***
Cardiac mortality (n/n with data on mortality)	41/1,101 [1]	45/759 [1]	53/480 [1]	17/153 [1]
adjusted for:	Reference			
-age and sex		1.54 (0.99-2.41)	3.31 (2.14-5.11)***	3.97 (2.06-7.65)***
- age, sex, LVEF and previous MI		1.34 (0.86-2.10)	2.40 (1.53-3.76)***	2.78 (1.43-5.41)**
- age, sex, LVEF, previous MI, diabetes and smoking		1.33 (0.85-2.08)	2.35 (1.50-3.69)***	2.70 (1.38-5.27)**
- age, sex and clinical depression		1.56 (1.00-2.43)*	3.53 (2.25-5.54)***	4.44 (2.27-8.69)***
Cardiovascular readmissions (n/n with data on readmissions)	333/1,094 [1]	294/737 [1]	194/457 [1]	57/146 [1]
adjusted for:	Reference			
-age and sex		1.40 (1.19-1.62)***	1.55 (1.29-1.86)***	1.45 (1.08-1.95)*
- age, sex, LVEF and previous MI		1.36 (1.15-1.61)***	1.45 (1.20-1.74)***	1.32 (0.98-1.78)
- age, sex, LVEF, previous MI, diabetes and smoking		1.36 (1.15-1.61)***	1.43 (1.18-1.72)***	1.30 (0.97-1.76)
- age, sex and clinical depression		1.41 (1.20-1.66)***	1.63 (1.33-2.01)***	1.58 (1.14-2.21)**

Abbreviations: BDI: Beck Depression Inventory, CI: Confidence Interval; HR: Hazard Ratio
*p<0.05, **p<0.01, ***p<0.001 with Cox regression
[1] Numbers represent the mean number of patients over the 10 imputed datasets

Depression status and cardiac outcomes

Table 4 shows cardiac outcomes associated with depression status. Compared to patients with BDI<10, those with BDI≥10 were at increased risk of all-cause and cardiac mortality, both in the absence and presence of clinical depression. Compared to patients with no clinical depression, those with clinical depression were at increased risk of all-cause and cardiac mortality. The dichotomized BDI-score was more strongly associated with cardiac mortality than with all-cause mortality, while clinical depression was somewhat more strongly associated with all-cause mortality than with cardiac mortality. Adjustment for LVEF and previous MI attenuated the risk of all-cause and cardiac mortality with 26 to 40%. Additional adjustment for smoking and diabetes attenuated this risk with another 2 to 7%. Adjusting for the continuous BDI-score attenuated the age-and sex-adjusted risk of all-cause mortality associated with clinical depression with 53%, and of cardiac mortality with 72%, rendering both to non-significant.

Compared to all-cause mortality and cardiac mortality, the increased risk of cardiovascular readmissions associated with depression status was substantially smaller and was only significant for the dichotomized BDI-score and not for clinical depression. In fact, the presence of clinical depression appeared to have a protective effect on the risk of cardiovascular readmissions associated with higher BDI-scores. For all three outcome measures, the proportional hazards assumption was met.

Table 3. Association of depression status at 3 months post-MI with demographical and clinical variables at baseline in 2,493 MI patients

	BDI<10 (n=1,618)	BDI≥10, no depression (n=479)	BDI≥10 and depression (n=396)	OR (95% CI) 2 versus 1	OR (95% CI) 3 versus 1	OR (95% CI) 3 versus 2
Age, mean (SD)[1]	61.0 (11.4)	63.4 (12.4)	58.2 (11.5)	1.02 (1.01-1.03)***	0.98 (0.97-0.99)***	0.96 (0.95-0.97)***
Female (%)[1]	19.4	26.6	27.6	1.51 (1.15-1.98)**	1.59 (1.22-2.08)**	1.06 (0.75-1.48)
Smoker at hospitalization (%)[1]	47.2	47.4	54.0	1.01 (0.81-1.26)	1.31 (1.04-1.65)*	1.30 (0.97-1.73)
Body mass index, mean (SD)[1]	26.7 (3.88)	26.6 (3.82)	26.4 (4.23)	1.00 (0.97-1.03)	0.99 (0.96-1.02)	0.99 (0.95-1.03)
Anterior site MI %[1]	32.4	36.5	34.1	1.20 (0.95-1.51)	1.08 (0.84-1.38)	0.90 (0.66-1.23)
Low LVEF (%) [1,3]	21.4	28.5	35.9	1.47 (1.14-1.88)**	2.06 (1.60-2.66)***	1.41 (1.03-1.92)*
Killip Class ≥ 2 (%)[1]	9.5	14.0	15.6	1.55 (1.12-2.14)**	1.76 (1.25-2.47)**	1.14 (0.76-1.70)
Previous MI (%)[1]	11.5	18.8	13.4	1.78 (1.29-2.43)***	1.19 (0.82-1.72)	0.67 (0.42-1.05)
PTCA during hospitalization (%)[2]	35.5	32.7	43.9	0.88 (0.70-1.11)	1.42 (1.11-1.82)**	1.61 (1.21-2.15)**
CABG during hospitalization (%)[2]	4.9	4.8	3.8	0.97 (0.59-1.61)	0.77 (0.41-1.43)	0.79 (0.38-1.65)
Diabetes (%)[1]	10.6	16.1	12.4	1.63 (1.20-2.22)**	1.20 (0.85-1.69)	0.74 (0.49-1.11)
Hypertension (%)[1]	31.7	35.2	35.0	1.17 (0.93-1.47)	1.16 (0.91-1.47)	0.99 (0.74-1.33)
Hypercholesterolemia (%)[1]	66.4	63.9	76.2	0.89 (0.70-1.13)	1.62 (1.23-2.13)**	1.82 (1.33-2.48)***
Peripheral vascular disease (%)[2]	6.2	9.9	10.9	1.65 (1.11-2.44)*	1.83 (1.23-2.72)**	1.11 (0.68-1.80)
Cerebrovascular disease (%)[2]	4.7	8.0	5.3	1.74 (1.08-2.78)*	1.11 (0.65-1.91)	0.64 (0.33-1.26)
Family history CAD (%)[1]	43.4	40.6	48.5	0.89 (0.71-1.12)	1.23 (0.97-1.55)	1.38 (1.04-1.84)*
Charlson Comorbidity Index, median (IQR) [2]	0 (0-1)	1 (0-2)	0 (0-2)	1.20 (1.10-1.31)***	1.16 (1.06-1.26)**	0.97 (0.87-1.07)
Medication at discharge (%)[2]						
- Aspirin	85.9	81.9	85.0	0.74 (0.55-1.00)	0.93 (0.67-1.30)	1.26 (0.85-1.87)
- Beta-blocker	84.9	80.9	82.3	0.75 (0.57-1.00)*	0.83 (0.59-1.15)	1.10 (0.76-1.59)
- Calcium antagonist	17.8	20.8	19.9	1.21 (0.93-1.58)	1.15 (0.84-1.58)	0.95 (0.66-1.36)
- Diuretics	13.0	21.3	15.5	1.80 (1.35-2.40)***	1.22 (0.86-1.74)	0.68 (0.44-1.04)
- Ace-inhibitor	40.8	42.9	40.5	1.09 (0.87-1.37)	0.98 (0.77-1.26)	0.90 (0.68-1.20)
- Statin	71.3	64.9	73.2	0.74 (0.58-0.95)*	1.10 (0.85-1.43)	1.48 (1.07-2.04)*
BDI at 3 months post-MI mean (SD)[1]	3.7 (2.8)	11.1 (5.9)	16.9 (15.7)	1.68 (1.59-1.78)***	1.86 (1.76-1.97)***	1.11 (1.08-1.14)***

Abbreviations: BDI: Beck Depression Inventory; CABG: Coronary Artery Bypass Graft; CAD: Coronary Artery Disease; CI: Confidence Interval; IQR: Interquartile Range; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; OR: Odds Ratio; PTCA: Percutaneous Transluminal Coronary Angioplasty; SD: Standard Deviation

*p<0.05, **p<0.01, ***p<0.001 with multinomial regression using patients with BDI<10 as reference group

[1] Mean, numbers and percentages represent the overall mean, the mean numbers and mean percentages over the 10 imputed datasets. SD's are calculated taking into account Rubin's rule.

[2] Mean, numbers, percentages and OR's are based on complete cases, because these variables were not included in the imputation model. PTCA n=2,382, CABG: n=2,379, peripheral vascular disease: n=2,481, cerebrovascular disease: n=2,478, Charlson Comorbidity Index: n=1,934; aspirin: n=2,441, beta-blocker: n=2,478, calcium antagonist: n=2,441, diuretics: n=2,478, ace-inhibitor: n=2,478, statin: n=2,478.

[3] LVEF<40% in DepreMI and LVEF<45% in MIND-IT

Recurrence, onset and severity of the depressive episode, depressive symptom profile and cardiac outcomes

Recurrence and onset of the depressive episode were not associated with any of the adverse outcomes. Severity of the depressive episode was associated with adverse outcomes, but reached significance only for all-cause mortality for patients with a severe depressive episode compared to those with a mild depressive episode. There cognitive/affective factor score of the BDI was significantly associated with all-cause mortality, somewhat less with cardiac mortality (non-significant), and not with cardiovascular readmissions. The somatic/affective factor score of the BDI was significantly associated with an increased risk of all three outcomes. Adjustment for LVEF and previous MI attenuated the risk associated with the somatic/affective factor score by 17 to 22%. Additional adjustment for diabetes and smoking did almost not affect further the risk of all three outcomes. Additional adjustment for the cognitive/affective factor score attenuated the risk of all-cause mortality with another 14%, of cardiac mortality with another 4%, but did not attenuate the risk of cardiovascular readmissions. For all outcomes the proportional hazards assumption was met.

Table 4. HR (95% CI) for cardiac outcomes associated with depression status at 3 months post-MI [1]

	BDI≥10, no depression vs BDI<10	BDI≥10 and depression vs BDI<10	depression vs no depression
All-cause mortality (HR (95% CI))	*120/479 vs 216/1,618[2]*	*71/396 vs 216/1,618[2]*	*71/396 vs 336/2,097[2]*
adjusted for age and sex	1.71 (1.35-2.17)***	2.02 (1.50-2.72)***	1.72 (1.29-2.30)***
adjusted for age, sex, LVEF and previous MI	1.49 (1.17-1.89)**	1.73 (1.29-2.32)**	1.53 (1.15-2.02)**
adjusted for age, sex, LVEF, previous MI, diabetes and smoking	1.46 (1.15-1.85)**	1.67 (1.25-2.24)**	1.48 (1.12-1.96)**
adjusted for age, sex and BDI-score	NA	NA	1.34 (0.89-2.03)
Cardiac mortality (HR (95% CI))	*57/479 vs 72/1,618[2]*	*27/396 vs 72/1,618[2]*	*27/396 vs 129/2,097[2]*
adjusted for age and sex	2.48 (1.72-3.57)***	2.26 (1.33-3.83)**	1.67 (1.01-2.77)*
adjusted for age, sex, LVEF and previous MI	1.95 (1.34-2.84)***	1.78 (1.06-2.99)*	1.40 (0.86-2.28)
adjusted for age, sex, LVEF, previous MI, diabetes and smoking	1.92 (1.32-2.79)**	1.73 (1.03-2.91)*	1.36 (0.84-2.21)
adjusted for age, sex and BDI-score	NA	NA	1.19 (0.65-2.18)
Cardiovascular readmissions (HR (95% CI))	*198/468 vs 542/1,604[2]*	*138/362 vs 542/1,604[2]*	*138/362 vs 740/2,072[2]*
adjusted for age and sex	1.34 (1.12-1.60)**	1.21 (0.99-1.49)	1.13 (0.93-1.38)
adjusted for age, sex, LVEF and previous MI	1.27 (1.06-1.52)*	1.14 (0.93-1.40)	1.08 (0.88-1.32)
adjusted for age, sex, LVEF, previous MI, diabetes and smoking	1.24 (1.04-1.49)*	1.14 (0.93-1.39)	1.08 (0.88-1.32)
adjusted for age, sex and BDI-score	NA	NA	0.96 (0.74-1.25)

Abbreviations: BDI: Beck Depression Inventory; CI: Confidence Interval; HR: Hazard Ratio; NA: not applicable

[1] Reference group are patients with no depressive symptoms (BDI<10: 216/1,618 all-cause mortality, 72/1,618 cardiac mortality, 542/1,604 cardiovascular readmissions)

[2] Numbers represent the mean number of patients over the 10 imputed datasets

*p<0.05, **p<0.01, ***p<0.001 with Cox regression analysis

Table 5: HR's (95% CI) for all-cause and cardiac mortality and cardiovascular readmissions associated with recurrence, onset and severity of the post-MI depressive episode and symptom profile of the depressive symptoms after MI [1]

	All-cause mortality	Cardiac mortality	Cardiovascular readmissions
First-ever (n=306) versus recurrent (n=96) depressive episode[2]			
Adjusted for age and sex	0.85 (0.43-1.70)	1.10 (0.28-4.27)	1.15 (0.72-1.84)
Post-MI onset (n=255) versus pre-MI onset (n=141) depressive episode[2]			
Adjusted for age and sex	0.74 (0.42-1.30)	0.70 (0.30-1.65)	1.16 (0.78-1.75)
Severity of the depressive episode (mild: n=118, moderate: n=177, severe: n=105)[2]			
Moderate vs mild			
Adjusted for age and sex	1.46 (0.72-2.95)	2.12 (0.62-7.27)	1.27 (0.84-1.93)
Severe vs mild			
Adjusted for age and sex	2.43 (1.21-4.92)*	2.87 (0.77-10.63)	0.96 (0.55-1.66)
Somatic/affective and cognitive/affective symptom dimensions (HR per SD increase, n=2,493 for mortality and n=2,434 for cardiovascular readmissions)			
Somatic/affective			
Model 1	1.29 (1.17-1.41)***	1.46 (1.27-1.69)***	1.12 (1.05-1.20)**
Model 2	1.23 (1.11-1.35)***	1.36 (1.17-1.59)***	1.10 (1.02-1.17)**
Model 3	1.22 (1.10-1.35)***	1.36 (1.16-1.58)***	1.09 (1.02-1.17)*
Model 4	1.18 (1.07-1.31)**	1.34 (1.14-1.57)***	1.10 (1.03-1.18)**
Cognitive/affective			
Model 1	1.19 (1.07-1.31)**	1.16 (0.99-1.36)	0.99 (0.92-1.06)
Model 2	1.18 (1.07-1.30)**	1.14 (0.97-1.33)	0.98 (0.91-1.05)
Model 3	1.18 (1.07-1.30)**	1.14 (0.97-1.33)	0.98 (0.91-1.05)
Model 4	1.12 (1.01-1.24)*	1.05 (0.91-1.22)	0.96 (0.89-1.03)

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; MI: Myocardial Infarction; SD: Standard Deviation

[1] Adjustments were made for: model 1: age and sex, model 2: age, sex, LVEF, previous MI, model 3: adjusted for age, sex, LVEF, previous MI, diabetes, and smoking, model 4: adjusted for age, sex, LVEF, previous MI, diabetes, smoking and the score on the other dimension (i.e. cognitive/affective or somatic/affective)

[2] Numbers are mean numbers over the 10 imputed datasets

Comments

The present study found self-reported depressive symptoms on the BDI to be a stronger predictor of adverse cardiac outcomes during a mean follow-up of 6 years after the MI than a diagnosis of clinical depression assessed by the CIDI. In fact, the increased risk associated with clinical depression could completely be explained by higher BDI-scores in patients with clinical depression. The

increased risk associated with depressive symptoms on the BDI could not be explained by clinical depression. The increased risk associated with BDI-scores was attributable to somatic/affective symptoms and less to cognitive/affective symptoms. Cardiac disease severity and risk factors explained one third to half of the increased risk associated with depressive symptoms on the BDI.

Our findings are consistent with two other studies that found self-reported depressive symptoms to be a stronger predictor for adverse cardiac outcomes than clinical depression obtained by a diagnostic interview (67, 101). The first study, including 222 MI-patients, found the risk of all-cause mortality the 18 months following MI associated with self-reported depressive symptoms to be much larger than with clinical depression (101). The other study found in 1,024 stable CHD patients self-reported depressive symptoms, but not clinical depression to be associated with new cardiac events (67). In contrast, two other studies found clinical depression to be stronger related to adverse cardiac outcomes than self-reported depressive symptoms (117, 223). Both studies found in sample sizes of respectively 450 and 804 stable CHD patients those with clinical depression to be at most increased risk of cardiac death and new cardiac events, followed by those with depressive symptoms only. None of these studies evaluated whether the risk associated with clinical depression could be explained by the level of self-reported depressive symptoms or vice versa. The present study was the first to evaluate whether adverse cardiac outcomes associated with clinical depression can be explained by higher levels of self-reported depressive symptoms.

The differential relation of self-reported depressive symptoms on the BDI and a diagnosis of clinical depression with cardiac outcomes suggests that the two have different underlying etiology. Moreover, in the present study, self-reported depressive symptoms on the BDI were a stronger predictor of cardiac related outcomes than of non-cardiac mortality, but clinical depression appeared to be relatively stronger related to non-cardiac mortality, which also suggests different underlying etiology. The substantial difference between the assessment of self-reported depressive symptoms on the BDI and the presence of a diagnosis of clinical depression with the CIDI may explain their difference in etiology. For instance, a depressive symptom that is a consequence of a physiological problem, such as the heart disease itself, will be identified when

using the BDI, but not when using the CIDI. In addition, the BDI includes symptoms that are not part of a DSM diagnosis of clinical depression. These 'extra' symptoms may have an etiology that differs from the etiology of the symptoms that build up a diagnosis of clinical depression in MI patients.

Another reason to believe that self-reported depressive symptoms and clinical depression have different underlying etiology is the age-difference between patients with elevated depressive symptoms and clinical depression. Patients reporting elevated depressive symptoms on the BDI in the absence of clinical depression were on average 5 years older than those with clinical depression. This is consistent with the trend found in the general population, where the prevalence of clinical depression decreases with age, but the prevalence of self-reported depressive symptoms may increase (212). This may be the result of the increasing prevalence of physical health problems with increasing age that will be reflected in self-reported depressive symptoms on a questionnaire, but not as symptoms making up a diagnosis of clinical depression established with a diagnostic interview.

The finding that elevated depressive symptoms on the BDI are predictive of adverse cardiac outcomes in the absence of a diagnosis of clinical depression suggests that also patients with sub-threshold depression can be at increased risk of adverse cardiac outcomes. By including only MI patients with clinical depression, RCT's evaluating the effects of antidepressant treatment may have excluded a high-risk group. If the prognostic impact of post-MI depression lies more in self-reported depressive symptoms than in clinical depression, this may explain why RCT's using clinical depression as an inclusion criterion found antidepressant treatment not to affect cardiac prognosis in MI patients (99, 128, 155). A more recent RCT evaluating the effects of antidepressant treatment using a collaborative care approach included MI- and unstable angina patients with BDI-scores ≥ 10 at hospitalization and at 3 months after the event. Compared to usual cardiac aftercare, they found the 6-month collaborative care program to be moderately effective in reducing depressive symptoms (effect size: 0.59), which also appeared to translate into better cardiac outcomes (228). The relatively optimistic results of this study may be due to the different inclusion criteria, but may also be due to the different type of intervention that was used.

Findings from the present study also suggest a major role for confounding in the association between depressive symptoms and cardiac outcomes, as one third to half of the association could be explained by cardiac disease severity and risk factors. Beyond the parameters that were adjusted for, other parameters of somatic health status were strongly associated with depressive symptoms in the present sample, such as the Charlson Comorbidity Index. Unfortunately, even though we used a very large sample of MI patients, the sample was still too small to be able to adjust for more covariates without introducing bias (192). It is likely that more of the association between depressive symptoms and cardiac outcomes could be explained by these other somatic health parameters. Also parameters that were not evaluated in the present study may underlie the increased risk of adverse cardiac outcomes associated with depression or depressive symptoms. In other studies, physical inactivity explained a fourth to a third of the association between depressive symptoms and risk of future cardiac events and mortality (67, 229). Thus, a major part of the association between depressive symptoms and cardiac prognosis may be explained by cardiac disease severity, somatic health status and physical inactivity. This could explain why traditional antidepressant treatments, such as SSRI's or CBT, do not improve cardiac prognosis in depressed MI patients (99, 128, 155). Instead, treatments targeting at the factors underlying the adverse cardiac outcomes associated with depressive symptoms may be more effective than the traditional antidepressant treatments. For instance, exercise training has been shown to be as effective as an SSRI in the treatment of major depression (230, 231). In addition, it substantially reduces the risk of adverse cardiac outcomes in cardiac patients (23). Cardiac rehabilitation has shown to reduce depressive symptoms substantially in cardiac patients (164). Depression in cardiac patients is, however, associated with less adherence to and completion of cardiac rehabilitation programs (70). Therefore, it seems of utmost importance that MI patients with elevated depressive symptoms are motivated to engage in physical activity and adhere to cardiac rehabilitation programs.

The increased risk of adverse cardiac outcomes associated with depressive symptoms was mainly due to the somatic/affective symptoms of depression on the BDI. This is consistent with previous studies (92, 177, 178),

contributing to the growing evidence that particularly somatic/affective symptoms of depression after MI are related to adverse cardiac outcomes. Somatic/affective depressive symptoms on the BDI are strongly related with a more severe cardiac disease and worse somatic health status (92, 177). The increased risk of new cardiac events and mortality associated with somatic/affective depressive symptoms could, however, not completely be explained by the cardiac disease severity and risk factors evaluated in the present study. Unmeasured parameters of physical health may partly explain the relation. For instance, somatic symptoms, but not cognitive symptoms of depression in stable CHD patients were found to be associated with decreased heart rate variability (232).

We found no increased risk of adverse cardiac outcomes associated with recurrence or onset of the depressive episode, adding to the inconsistent literature in this field (214). Our findings are particularly comparable to those of Glassman et al, who found recurrence and onset of the depressive episode not to be related to mortality in 369 depressed acute coronary syndrome patients (155). However, they are inconsistent with a study that found an increased risk of all-cause mortality associated with first-ever depression in 920 depressed MI-patients (171). It is difficult to explain these discrepant findings, but they may be due to the difficulties in assessing a history of depression.

The present study has several strengths. It evaluated the impact of both self-reported depressive symptoms on a questionnaire and a diagnosis of clinical depression obtained with an interview on adverse cardiac outcomes in the largest sample of MI patients to date. Due to the large sample size and long follow-up duration, the number of adverse outcomes was sufficient to adjust for covariates without introducing bias. There are also some limitations. First, no information is present on whether the patient received treatment for depression during the follow-up period. It could be that compared to those with elevated BDI scores, those with clinical depression were more likely identified by providers or were more aggressively treated during follow-up, which could explain the relatively better cardiac outcomes in this group. Another limitation is the potential presence of selection bias because patients with missing data on mortality were more likely to have had a previous MI, hypercholesterolemia and cerobrovascular disease than those with data on mortality. However, less than

7% of the sample had missing data on mortality. Finally, patients enrolled in MIND-IT scoring below 10 on the BDI were not assessed for clinical depression. Therefore, we missed some cases of clinical depression. However, the negative predictive value of BDI-scores>=10 is about 2% (151), thus in 2% of patients scoring <10 on the BDI clinical depression would be present, which would be 32 out of the 1,618 patients in the present sample. We assume that it is not likely that these patients would have substantially affected the results.

The present study was the first to evaluate whether self-reported depressive symptoms predict adverse cardiac outcomes independent from the presence of a diagnosis of clinical depression, and vice versa. In a sample of 2,493 MI patients, self-reported depressive symptoms on the BDI predicted new cardiac events and mortality independent from the presence of a diagnosis of clinical depression established with the CIDI. In fact, the increased risk associated with clinical depression could completely be explained by higher levels of self-reported depressive symptoms in patients with clinical depression. This suggests that self-reported depressive symptoms on the BDI have a different etiology than clinical depression established with the CIDI in MI patients. The association between BDI-scores and cardiac outcomes was mainly due to somatic/affective depressive symptoms. A third to half of the association between BDI-scores and cardiac outcomes could be explained by cardiac disease severity and risk factors in the present study, but it is likely that somatic health status and physical inactivity explain more of the association.

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Chapter 9

Vital exhaustion: a symptom dimension of depression in myocardial infarction patients?

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Submitted

Abstract

Background: Depression and vital exhaustion are independent risk factors for cardiovascular disease. It remains unclear to what extent the two concepts overlap. We hypothesized that vital exhaustion overlaps more with somatic depression than with cognitive depression.

Methods: A total of 528 myocardial infarction (MI)-patients were administered the Beck Depression Inventory (BDI) and the Maastricht Questionnaire (MQ) at hospitalization and 3, 6 and 12 months afterwards. Factor analysis on the BDI yielded a somatic/affective and cognitive/affective factor. Whether vital exhaustion overlaps more with the somatic/affective factor than with the cognitive/affective factor was assessed by: 1) calculating correlation coefficients, 2) examining the comparability in their association with the risk of new cardiovascular events, and 3) assessing the comparability in the course over time after index MI.

Results: Vital exhaustion correlated significantly stronger with the somatic/affective (ρ=0.76-0.83) than with the cognitive/affective factor (ρ=0.30-0.46) at all four time points ($p<0.001$). The HR (95% CI) for new cardiovascular events associated with vital exhaustion (1.39 (1.16-1.66)) was more comparable to that of the somatic/affective factor (1.43 (1.21-1.70)), than the cognitive/affective factor (1.12 (0.92-1.35)). One standard deviation (SD) change over time in the somatic/affective factor was associated with 0.52 SD change (SE 0.02) in vital exhaustion. One SD change in the cognitive/affective factor was associated with 0.24 SD (SE 0.02) change in vital exhaustion.

Conclusions: Vital exhaustion overlaps more with somatic than with cognitive symptoms of depression. Our findings support that vital exhaustion and somatic depression may represent the same underlying concept.

Introduction

The prevalence of depression in patients suffering from heart disease is much higher than in the general population (233, 234). As heart disease and depression are predicted to be the number one and two diseases contributing to the global burden of disease by 2020 (235), it is pivotal that the relationship between the two is well understood.

Vital exhaustion has been developed as a construct describing symptoms of fatigue, irritability and demoralization, both as a precursor and a consequence of acute coronary syndrome (236, 237). Vital exhaustion is a risk factor for the development and progression of cardiovascular disease (182, 238), but it is unclear to what extent it reflects the same as depression. To date, studies evaluating the overlap between depression and vital exhaustion have generated inconsistent results. Three studies found evidence supporting a 2-factor model in which depression and vital exhaustion are two different concepts (239-241). The first study found the prevalence of depressed mood to be very low in patients with vital exhaustion (241). The second found depression to relate more to psychiatric factors, whereas vital exhaustion related more to cardiac disease factors (239). The third study performed a factor analysis on a depression questionnaire and a short version of the Maastricht Questionnaire (MQ) that assesses vital exhaustion, and found them to be representing different underlying constructs (240). However, one other study found strong correlations between scores on depression questionnaires and the MQ (242). A potential explanation for the discrepancies between findings from the first three studies and this last study may be the heterogeneity of depression. For instance, Van Diest and Appels found vital exhaustion not to be related to depressed mood, but strongly related to the individual items 'fatigability', 'work inhibition', 'sleep disturbances' and 'loss of libido' of the Beck Depression Inventory (BDI) (241).

Previously, we described two different symptom dimensions of depression in MI-patients: a somatic/affective and a cognitive/affective dimension (92). Somatic/affective symptoms are remarkably stronger associated with new cardiac events than cognitive/affective symptoms (92, 177,

178). Those items from the BDI relating to vital exhaustion in the study by Van Diest and Appels are in fact those items loading mainly on the somatic/affective dimension, whereas the items that did not relate to vital exhaustion in the study by Van Diest and Appels loaded mainly on the cognitive/affective dimension. Apparently, many symptoms defining vital exhaustion show a considerable conceptual overlap with the somatic/affective symptoms of the BDI. If this is empirically supported, perhaps vital exhaustion might be regarded as a symptom dimension of depression, which would help to translate research findings from these separate lines of research. In this study, we therefore evaluated whether vital exhaustion overlaps more with the somatic/affective than the cognitive/affective symptom dimension of depression in a sample of MI patients.

Methods

Data from the Depression after Myocardial Infarction (DepreMI) study were used. The methods of this study have been described in detail elsewhere (175, 243), and are briefly described below.

Design and patients

The DepreMI was a naturalistic follow-up study on the impact of depression on cardiac prognosis in MI patients. Subjects were recruited from four hospitals in the north of the Netherlands. From September 1997 and October 2000, all consecutive patients admitted for MI were assessed for eligibility. Inclusion criteria, of which at least two had to be met, were a) chest pain for at least 20 minutes, b) creatinine phosphokinase levels 100% above normal or creatinine phosphokinase MB levels above 10%, and c) presence of new pathological Q waves on the electrocardiogram in at least two leads. Exclusion criteria were life expectancy of less than a year because of non-cardiac condition, too poor physical condition according to hospital staff, cognitive dysfunction, inability to speak or read Dutch, occurrence of an MI in patients admitted for another

reason, and follow-up visits scheduled in a non-participating hospital. All participating patients in the study signed an informed consent form and the ethics committee review board at all the participating hospitals approved the study protocol.

Assessment of depressive symptoms, vital exhaustion

Depressive symptoms were measured using the BDI (244) during hospital stay and at 3, 6 and 12 months post-MI. The BDI is a widely used 21-item self-report measure assessing the presence and severity of depressive symptoms. Participants were instructed to rate each symptom on a scale from 0 to 3, with a score of 0 representing absence and scores 1-3 representing increasing levels of severity. Total scores can range from 0 to 63, with a score of 10 or more indicating at least mild depressive symptoms.

Vital exhaustion was assessed at the same time points using the MQ (237). The MQ is a 21-item questionnaire, originally developed to identify future cases of coronary heart disease (181). Each statement may be answered Yes, No or Don't Know, resulting in a score from 0 to 2. Total scores range from 0 to 42, with a score of 14 or more suggesting significant symptoms of vital exhaustion.

Assessment of new cardiovascular events

Cardiovascular mortality and cardiac-related readmissions to the hospital were obtained from hospital records and the participant's primary care physician. An independent endpoint committee consisting of two cardiologists evaluated whether potential endpoints were cardiovascular or not. Follow-up time started at the index-MI and lasted up until a) the occurrence of cardiovascular complication, b) end of follow up time. Mean follow up time was 2.5 years (SD=0.9). Patients without an event were censored at the end of follow up date or date of death (in case of non-cardiac death).

Data analyses

Principal Component Analysis (PCA) with oblimin rotation was performed on all 21 items of the BDI at all four time-points to obtain the symptom dimensions of depression. Based on a scree-plot the optimal number of factors was two, representing somatic/affective and cognitive/affective symptoms. The correlation between the two factors was 0.34. Factor loadings on the two dimensions are shown in Table 1. Using the regression method, standardized total factor scores were calculated for the somatic/affective and cognitive/affective symptom dimensions.

Whether the overlap between vital exhaustion and the somatic/affective dimension of the BDI was greater than the overlap between vital exhaustion and the cognitive/affective dimension of the BDI was assessed in three steps: First, Spearman correlation coefficients were calculated in order to evaluate the association between (a) vital exhaustion and the factor score on the somatic/affective symptom dimension, and (b) vital exhaustion and the cognitive/affective symptom dimension at each of the four time points. Whether the two correlation coefficients differed significantly from each other was tested using Steiger's formula for comparing two correlation coefficients from two dependent samples (245). Second, Cox proportional hazard regression analyses were used to examine the risk of new cardiovascular events associated with (a) the total score of the MQ, (b) the factor score on the somatic/affective symptom dimension of the BDI, and (c) the factor score on the cognitive/affective symptom dimension of the BDI during hospitalization for the index-MI. As the BDI symptom dimensions had standardized distributions, the score on the MQ was z-transformed for the sake of interpretation and comparability. Third, we assessed whether the course over time after the index MI of the standardized vital exhaustion score was more similar to that of the somatic/affective symptom dimension than of the cognitive/affective symptom dimension of the BDI. For each scale the difference in scores between each consecutive time-point was calculated. Since there were four time-points, this resulted in three difference-scores per scale. With mixed model analysis we evaluated the independent effects of the difference-scores of the somatic/affective and cognitive/affective symptom dimensions on the difference-scores of the MQ.

Results

Sample

A total of 528 MI patients gave informed consent. BDI scores at 0, 3, 6 and 12 months were present for 509, 514, 493 and 492 patients respectively. MQ scores at 0, 3, 6 and 12 months were present for 520, 514, 493 and 492 patients respectively. For 464 patients data on new cardiac events was present. Of these, 110 (23.7%) had a new cardiac event during a mean (standard deviation (SD)) follow-up time of 2.03 (1.02) years.

Correlation of symptom dimension factors with vital exhaustion

Table 1 shows for the somatic/affective and cognitive/affective factor scores the factor loadings from the pattern matrix.

As shown in Table 2, vital exhaustion correlated strongly and significantly with both the somatic/affective factor score and the cognitive/somatic factor score on all four time points, but the correlation was stronger for the somatic/affective than for the cognitive/affective factor score. Steiger's formula confirmed that the two correlation coefficients differed significantly from each other ($p<0.001$ for t=1, t=2, t=3 and t=4).

Association of the symptom dimensions and vital exhaustion with new cardiovascular events

Figure 1 shows Kaplan Meier curves showing the risk of new cardiovascular events for the 20% of patients scoring highest on each of the three scales compared to the other patients. Per SD increase in the somatic/affective factor score, the HR (95% CI) for new cardiovascular events was 1.43 (1.21-1.70; $p<0.001$). For vital exhaustion this was 1.39 (1.16-1.66;$p<0.001$) and for the cognitive/affective factor score 1.12 (0.92-1.35; $p=0.261$).

Table 1. Factor loadings of depressive symptom dimensions and relation to BDI items

Depressive symptoms from BDI	Dimensional structure in de Jonge et al. (2006)		Dimensional structure in Martens et al. (2009)		Dimensional structure in the present study	
	Som/Aff	Cog/Aff	Som/Aff	Cog/Aff	Som/Aff	Cog/Aff
Sadness	0.64	0.45	0.48	0.57	0.32	0.51
Pessimism	0.56	0.58	0.48	0.36	0.38	0.42
Sense of failure		0.66	0.72	0.67		0.74
Dissatisfaction	0.69	0.49		0.38	0.58	0.31
Guilt		0.70		0.71		0.75
Punishment		0.59		0.67		0.64
Self-dislike		0.72		0.69		0.66
Self-accusations		0.71		0.65		0.68
Suicidal ideas		0.49	0.35	0.52		0.33
Crying	0.52		0.39	0.32		0.45
Irritability	0.45		0.39	0.32	0.35	
Social withdrawal	0.42	0.51	0.34		0.33	0.34
Indecisiveness	0.68	0.40	0.54	0.35	0.54	
Body-image change		0.57	0.42	0.32		
Work difficulty	0.69		0.76		0.71	
Insomnia	0.55		0.59		0.51	
Fatigability	0.58		0.65		0.70	
Loss of appetite	0.42		0.50		0.60	
Weight loss					0.33	
Somatic preoccupation	0.67		0.51		0.44	0.31
Loss of libido	0.50		0.60	0.42	0.60	

BDI: Beck Depression Inventory, Cog/Aff: Cognitive/affective factor, Som/Aff: Somatic/affective factor

Table 2. Spearman correlations between somatic/affective symptoms, cognitive/affective symptoms and vital exhaustion scores at hospital stay and 3, 6 and 12 months post-MI

	Som/Aff		Cog/Aff		Steiger's formula	
MQ	rho	p	rho	p	Z	p
hospital stay	0.76	<0.001	0.30	<0.001	10.7	<0.001
3 months	0.83	<0.001	0.42	<0.001	12.5	<0.001
6 months	0.83	<0.001	0.46	<0.001	11.3	<0.001
12 months	0.82	<0.001	0.43	<0.001	11.8	<0.001

Cog/Aff: Cognitive/affective factor, MI: Myocardial Infarction, MQ: Maastricht Questionnaire, Som/Aff: Somatic/affective factor

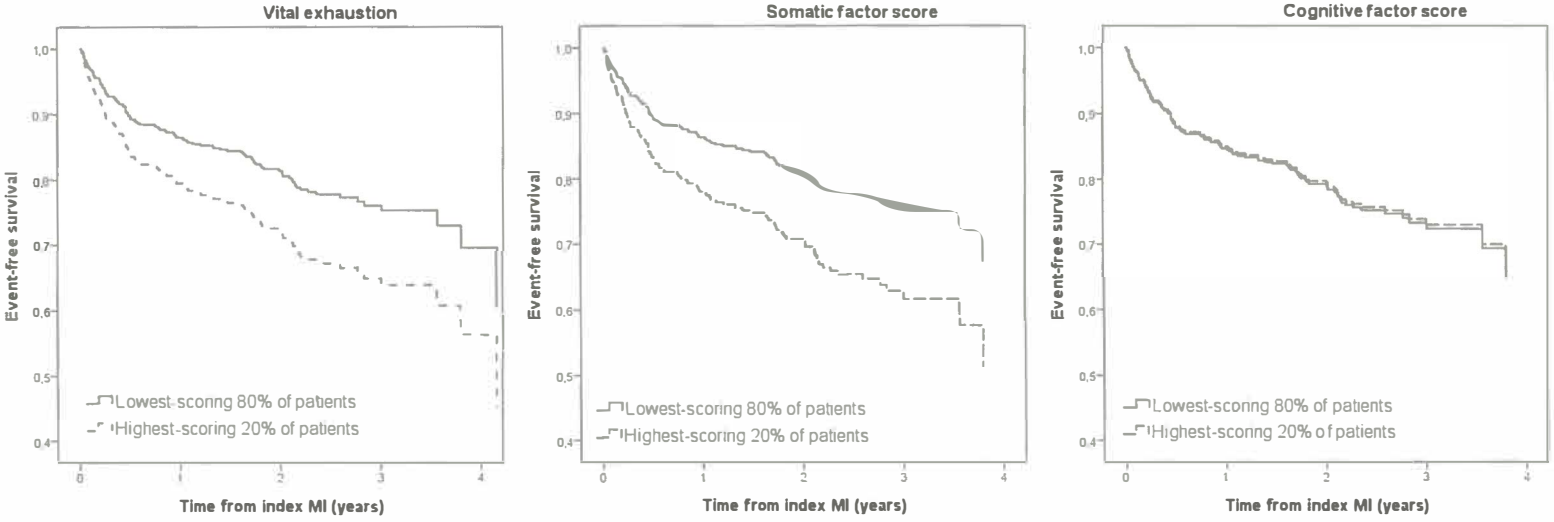

Figure 1. Event-free survival following MI and relationship to somatic/affective symptoms, cognitive/affective symptoms and vital exhaustion score

Course over time of vital exhaustion and symptom dimension factors

Mixed model analysis showed that an increase of 1 SD in the difference score of the somatic/affective factor of the BDI was associated with an increase of 0.52 SD in the MQ (standard error (SE) 0.02, p<0.001). An increase of 1 SD in the difference score of the cognitive/affective factor of the BDI was associated with an increase of 0.24 SD in the MQ (SE 0.02, p<0.001). Adjusted for the cognitive/affective factor of the BDI, a rise of 1 SD in the difference score of the somatic/affective factor of the BDI was associated with an increase of the MQ score of 0.50 SD (SE 0.02, p<0.001). After adjustment for the somatic/affective factor an increase of 1 SD of the cognitive/affective factor was associated with an increase of the MQ score by 0.20 SD (SE 0.02, p<0.001).

Discussion

The present study examined the overlap between vital exhaustion and two symptom dimensions of depression in MI patients. First, the correlations between vital exhaustion and somatic/affective symptoms were significantly stronger than the correlations between vital exhaustion and cognitive/affective symptoms at all four time points. Second, the somatic/affective symptom dimension, but not the cognitive/affective symptom dimension, showed a practically identical association with new cardiovascular events to vital exhaustion during hospitalization for the index MI. And third, the course over time after MI was more comparable for vital exhaustion and the somatic/affective dimension than for vital exhaustion and the cognitive/affective dimension. These results support the hypothesis that vital exhaustion overlaps more with somatic than with cognitive symptoms of depression.

The results of this study may explain the inconclusive results of previous studies evaluating the overlap between vital exhaustion and depression. Van Diest and Appels (241) concluded vital exhaustion and depression to be different. Also the study by Kopp and colleagues (239) supported the 2-factor

model since they found depression and vital exhaustion to be differently related to behavioural risk factors for coronary artery disease. Both findings can be explained by vital exhaustion overlapping with only a part of depression. This could account for the lack of depression in vitally exhausted individuals, as persons with a high score on the somatic/affective factor of the BDI might not show all the symptoms of depression as is needed for a diagnosis of major depressive disorder. It could also explain the differential associations between depression and vital exhaustion with behavioural risk factors found by Kopp et al., as this could differ among the symptom dimensions of depression itself. Wojciechowski and colleagues (242) found evidence contradictory to the prior two studies and concluded that depression and vital exhaustion are best described as a single concept. They found strong correlations between vital exhaustion and depression at four different time points and reported a single factor using principal components analyses. However, as they used the Zung-SDS and the SCL-90 to assess depressive symptoms, it is unclear to what extent these findings concern the somatic/affective or cognitive/affective dimensions.

The assessment of the overlap of vital exhaustion with different dimensions of depression in this study was the first to our knowledge, and we believe these findings can have important implications. Our results suggest that vital exhaustion and somatic depression may cover the same concept, which is particularly associated with poor cardiac outcomes. This concept is different from major depressive disorder (MDD), since patients suffering from vital exhaustion do not necessarily need fulfill all criteria for MDD (241) and, similarly, somatic symptoms of depression can be present in the absence of a diagnosis of MDD.

Findings from some studies suggest that inflammation may underlie the vital exhaustion and somatic depression in MI patients. Janszky and colleagues (246) found in women with coronary heart disease that vital exhaustion showed an association with inflammation measured, whereas depression did not. In other studies, depression was associated with inflammation which has been proposed as one of the pathways between depression and poor cardiac outcomes (247). For instance, Dantzer and colleagues (248) reported a direct increase particularly in somatic depression after cytokine immunotherapy in patients treated for cancer or hepatits C.

A more direct implication of this study is the possibility to integrate study findings concerning vital exhaustion and the somatic/affective symptom dimension of depression in MI patients. An intervention consisting of group therapy and relaxation exercises has been shown to reduce vital exhaustion, but not the risk of a new cardiac event (249). The same might be true for somatic depression. Holzapfel and colleagues (250) compared depressive symptom profile between depressed congestive heart failure (CHF) patients and depressed patients without CHF. They found no difference in the prevalence of somatic symptoms, but CHF patients showed less depressed mood and feelings of worthlessness and guilt than those without CHF. Exactly these symptoms might be absent in patients suffering from vital exhaustion, as Van Diest and colleagues found (241).

In conclusion, the present study revealed that vital exhaustion strongly overlaps with somatic and much less so with cognitive depression. Our findings suggest that somatic depression symptoms and vital exhaustion may represent the same underlying concept, which is particularly associated with poor cardiac outcomes, and thus that vital exhaustion may be regarded as a symptom dimension of depression.

Chapter 10

Discussion

The present thesis focused on depression after MI as a risk factor for new cardiac events and mortality. Chapters 2 and 3 showed that antidepressant treatment trials in depressed MI patients failed to improve cardiac prognosis. In Chapters 5 to 9 two possible reasons for this were investigated. The first reason hypothesized that depression after MI is heterogeneous: that is, the existence of a subtype of depression that is both treatment-resistant and cardiotoxic could explain why antidepressant treatment appeared not to affect cardiac outcomes. The second reason hypothesized that it is not depression that is predictive of worse prognosis, because post-MI 'depression' is a reflection of an underlying factor that causes new cardiac events and mortality, such as the severity of the heart disease. This could happen because symptoms of the heart disease itself, such as fatigue, overlap with symptoms of depression. Since antidepressant treatment in general is not aimed at cardiac disease severity, it does not affect the cardiac prognosis. Furthermore, the worse prognosis associated with post-MI 'depression' could also be present in patients not meeting criteria for major depression after MI. By including only patients with major depression, the antidepressant treatment trials may have excluded a group of MI patients also at risk of worse prognosis.

Heterogeneity of post-MI depression: Does the existence of a cardiotoxic, treatment-resistant subtype of depression explain why treatment for depression does not improve cardiac prognosis?

First-ever and new onset depression are not necessarily cardiotoxic, but treatment-resistant depression is

In Chapter 5 it was found that MI patients with a first-ever depressive episode that was also treatment-resistant have the highest risk of new cardiac events or mortality. Having a recurrent depressive episode that responded to antidepressant treatment was associated with the lowest risk of new cardiac events or mortality. Although from this and other studies there appeared to be a tendency for first-ever and new onset depressive episodes to be a cardiotoxic

subtype of depression, in Chapter 6 we found in our systematic review that there is in fact no consistent evidence for such a tendency. In addition, in Chapter 8, patients with first-ever and new onset depression were not at increased risk of new cardiac events or mortality up till 10 years after the MI compared to those with recurrent and pre-MI onset depression. Thus no firm conclusion can be made about whether first-ever and new onset depression is a cardiotoxic subtype of depression. Also the hypotheses explaining why first-ever depression would be a high-risk subtype of depression have been contradicted in the literature. For instance, the vascular depression hypothesis proposes that atherosclerosis causes depression (207, 251). It was therefore thought that more severe atherosclerosis underlies depressions occurring for the first time late in life, potentially explaining the worse cardiac prognosis for MI patients with first-ever depression. Although cross-sectional, retrospective and small studies found severity of atherosclerosis to be associated with late-life depression (173, 174, 252-254), severity of atherosclerosis was not predictive of developing a major depression or depressive symptoms late in life in a longitudinal study (255, 256). Furthermore, in a large sample of depressed MI patients participating in ENRICHD, those with first-ever depression had no worse underlying heart disease than patients with recurrent depression and there were no differences between patients with first-ever and recurrent depression in response to antidepressant treatment (171). Thus, the evidence is not consistent in that first-ever and new onset depression are treatment-resistant and cardiotoxic subtypes of depression. This does not mean that post-MI depression is not heterogeneous, because the literature has been more consistent in showing the cardiotoxicity of treatment-resistant and persistent depression (154, 155, 161, 187). Below, I will present two possible explanations for the presence of treatment-resistant or persistent depression in MI patients and how the existence of MI patients with treatment-resistant or persistent depression can explain why antidepressant treatment trials did not improve cardiac outcomes.

Two potential reasons for the cardiotoxicity of treatment-resistant depression

The first reason is that depression after MI is at least partly a reflection of the heart disease. A constantly severe or deteriorating heart disease would be reflected in a depression that persists and would also explain the worse prognosis. Furthermore, if the depression is a reflection of the underlying heart disease, then this would explain why antidepressant treatments, that do not target the heart disease, do not improve the depression. The second reason is that depressed MI patients who are non-adherent to their antidepressant treatment are also more likely to be non-adherent to cardiac aftercare regimens. Non-adherence to antidepressant treatment may explain why the depression does not improve with antidepressant treatment and non-adherence to the cardiac aftercare regimens could explain their worse cardiac prognosis. Below, the two mechanisms are explained in the light of the results presented in this thesis and the literature.

Depression after MI is a reflection of the severity of the underlying heart disease

In Chapter 7 it is shown that an increase in depressive symptoms just after MI predicts worse cardiac prognosis independent from the number of depressive symptoms just before MI. One plausible explanation for the worse prognosis associated with an increase in depressive symptoms just after MI, is that an increase in depressive symptoms just after MI has an etiology related to the MI. For example, it may be a reflection of the simultaneous deterioration in the condition of the heart due to a more severe MI. The deteriorated condition of the heart, in turn, may explain the worse prognosis associated with an increase in depressive symptoms. An increase in depressive symptoms was associated with a more severe heart disease, but adjustment for the heart disease severity did not explain the worse prognosis in patients with an increase in depressive symptoms. Chapter 8 showed that a third to half of the increased risk of new cardiac events and mortality associated with depressive symptoms could be explained by the severity of the heart disease. This is consistent with results from a meta-analysis, in which it was found that statistical adjustment for left ventricular ejection fraction reduced the association between depression and

cardiac prognosis with 45% (57). Although this appears to be a substantial part of the association, still more than half of the association appeared *not* to be explained by the severity of the heart disease. This does not necessarily mean that the severity of the heart disease does not underlie this other part of the association. Statistical adjustment for underlying factors is often imprecise and incomplete, meaning that an underlying factor in reality explains more of the association than statistical adjustment can identify (205). Left ventricular ejection fraction, which is assessed in most studies, is a good measure for the severity of the heart disease, but it is not the only measure. Unmeasured parameters of heart disease severity, such as severity of atherosclerosis, may explain more of the association between depression and prognosis. In addition, no parameter is assessed perfectly accurate. A parameter (for example left ventricular ejection fraction) is often not the perfect measure for the factor that is intended to be measured (for example heart disease severity). Measurement errors are likely and continuous parameters are sometimes categorized. Statistically adjusting for imprecise measures of an underlying factor, therefore, weakens the strength of an association less than it explains the association in reality (205). Thus, incomplete and imprecise measurement of heart disease severity must underestimate its underlying role in the association between depression and prognosis. Therefore, heart disease severity may still underlie the worse prognosis associated with an increase in depressive symptoms after MI found in Chapter 7, and it explains probably more than 45% of the association between depression and cardiac prognosis.

Treatment non-adherence and lifestyle factors

Non-adherence of the patient to antidepressant treatment may explain why depression after the MI does not improve with the treatment. Patients who are non-adherent to antidepressant treatment are probably also more likely to be non-adherent to cardiac aftercare regimens, which includes modifying lifestyle, adherence to cardiac medications, following and completing cardiac rehabilitation programs and attending follow-up visits in the hospital. Non-adherence to both antidepressant treatment and cardiac aftercare regimens could explain why particularly patients with treatment-resistant depression have worse cardiac prognosis. Compared to non-depressed heart disease

patients, those with depression are less likely to change lifestyle behaviors, such as smoking cessation and engaging in physical activity (67-69), less often complete cardiac rehabilitation programs (70, 257, 258), and are less adherent to cardiac medications (62). In heart disease patients, a healthy lifestyle is a crucial predictor for better cardiac prognosis. Heart disease patients who stop smoking after MI have a 36% reduced mortality rate compared to those who continue smoking (22). A meta-analysis of randomized controlled trials showed that cardiac rehabilitation programs with exercise therapy reduce cardiac mortality rates by 26% (23). In addition, exercise training has been shown to be as effective as antidepressant medications in the treatment of major depression (230, 231). In heart disease patients, cardiac rehabilitation and exercise programs lead to great reductions in depression, but this needs to be confirmed in a randomized controlled trial (164, 165, 259). Finally, physical inactivity has been found to explain about a third to a fourth of the association between depression and cardiac prognosis in healthy individuals and cardiac patients (67, 229). The intrinsic motivation to care for the health thus appears an important factor in depressed MI patients. This is also reflected in Chapter 3 that identified increased mortality rates in depressed MI patients who did not receive antidepressant treatment, compared to those who did. Less intrinsic motivation to care for their health is a potential reason why patients in MIND-IT chose not to be treated for the depression. In turn, less intrinsic motivation to care for their health could explain the increased mortality rates for those not receiving treatment for depression. One other study also found, in a non-randomized comparison, better cardiac prognosis for depressed individuals who received antidepressant treatment compared to those who did not, which could also be due to differences in the intrinsic motivation to care for their health (162). Thus, patients' intrinsic motivation to care for their health, resulting in compliance to cardiac aftercare regimens and modifying lifestyle may be very important in the association between depression, and particularly treatment-resistant depression, and cardiac prognosis. In turn, the existence of a non-adherent, treatment-resistant and high-risk subgroup of depressed MI patients could partly explain why antidepressant treatment trials found no improvements in cardiac prognosis associated with antidepressant treatment.

It is not depression that predicts poor cardiac prognosis in MI patients

It may not be depression itself that predicts poor cardiac prognosis in MI patients. First, the increased risk could also be present in MI patients not meeting criteria for major depression after the MI. Second, depression after MI may be nothing more than a reflection of one or more underlying factors that cause the increased risk of poor cardiac prognosis.

The increased risk lies not in major depression itself

Chapter 7 showed that an increase in number of depressive symptoms just after MI is associated with worse cardiac prognosis independent from the number of symptoms just before the MI. This means that an increase in depressive symptoms just after MI is similarly associated with cardiac prognosis in the following three situations: 1) when it leads to a new diagnosis of depression after the MI (i.e. in patients with new onset depression), 2) when it leads to no depression after MI (i.e. in patients not meeting criteria for major depression after MI), or 3) when it occurs on top of a pre-existing depressive episode (in patients with pre-MI onset depression). This means that not only patients with new onset depression have worse cardiac prognosis, also patients with only subthreshold depressive symptoms and patients with pre-MI onset depression may be at increased risk of new cardiac events as long as there is an increase in depressive symptoms just after MI. Chapter 8 shows that depressive symptoms reported by the patient on a questionnaire appear a stronger predictor of poor cardiac prognosis than major depression established with a diagnostic interview. The increased risk associated with elevated depressive symptoms could mainly be attributed to the somatic depressive symptoms. In Chapter 9 it is shown that somatic symptoms of depression overlap substantially with vital exhaustion and that both constructs are strongly associated with worse cardiac prognosis. Thus the cardotoxicity of post-MI 'depression' appears not to lie in major depression only. Clinical trials included in the systematic review (151) have only included patients with major depression. Therefore, they have excluded a high-risk subgroup of patients which made these trials less suitable to evaluate the effects of antidepressant treatment on cardiac prognosis.

Residual and unmeasured confounding

Studies that found depression to be associated with worse cardiac prognosis have all been observational studies. One problem with the design of observational studies is that the associations that are found may be confounded by factors underlying the association. Thus depression may in fact be a reflection of an underlying risk factor, for instance the heart disease itself, that predicts the poor prognosis. As previously described, statistical adjustment for heart disease severity may lead to an underestimation of its underlying role, because of imprecise and incomplete measurement of heart disease severity parameters. This phenomenon is known as residual (i.e. due to imprecise measurement of parameters) or unmeasured (i.e. due to unmeasured parameters) confounding (205). A simulation study showed that associations found in observational studies, such as that between depression and cardiac prognosis, can be generated by residual and unmeasured confounding alone (260). In contrast to observational studies, experimental studies with a randomized design minimize confounding by unmeasured as well as measured factors. If an association is found in an observational study, but cannot be identified in an experimental study, then it is likely that unmeasured or imprecisely measured factors confound the association. This may also be the case for depression and cardiac prognosis. Observational studies consistently found an association between depression and cardiac prognosis, but experimental manipulation of the depression in a randomized trial does not affect cardiac prognosis. Thus the association between depression and cardiac prognosis found in observational studies may be due to unmeasured and residual confounding which explains why manipulating the depression in antidepressant treatment trials did not improve the cardiac prognosis. As previously described, heart disease severity could be one important confounding factor, but also other factors, such as inflammation or overall physical health status, may confound the association. The antidepressant treatments in heart disease patients did not aim to improve these underlying factors and may therefore not have improved cardiac prognosis.

Antidepressant treatment had only modest effects on depression itself

One complicating factor in the argumentation of residual and unmeasured confounding is that the randomized trials modified the depression itself only modestly. Therefore, another reason why the antidepressant treatment trials did not improve cardiac prognosis may be that the modification of the depression was too small to lead to a modification in the cardiac prognosis. The fact that only small improvements in depression could be achieved makes it difficult to evaluate a question that plays a prominent role in the field of depression and heart disease: namely whether depression after MI is causally related to cardiac prognosis. To be able to evaluate whether depression is causally related to cardiac prognosis, it must be possible to experimentally modify the depression in order to evaluate whether this also leads to changes in the cardiac prognosis. Too small improvements in depression could make it difficult or maybe even impossible to identify changes in cardiac prognosis. One potential way to get round this problem would be to evaluate whether improvements in depression lead to improvements in cardiac prognosis in subgroups of depressed MI patients who are known to respond better to antidepressant treatment. For instance, greater response rates have been found in depressed patients with more previous depressive episodes compared to those with less previous depressive episodes (261-263), but this needs more study in MI patients.

Interpretation of findings

Two major pathways appear to underlie the association between depression after MI and cardiac prognosis. First, depression after MI, and in particular somatic depressive symptoms and persisting depression, may be a reflection of a more severe heart disease. Treatments not aimed at improving the heart disease therefore do not improve the depression in these patients. Second, depression may be associated with non-adherence to antidepressant treatments and cardiac aftercare regimens, explaining the particular increased risk associated with treatment-resistant depression. Antidepressant treatments only improve cardiac prognosis if they affect coping styles that improve the

adherence. The prognostic value of depression particularly lies in somatic depressive symptoms, which overlap substantially with vital exhaustion, and is also present in MI patients not meeting criteria for major depression. **Figure 1** represents a model that integrates findings of the present thesis with the literature, showing the two major pathways that underlie the association between depression and cardiac prognosis: severity of the heart disease and treatment non-adherence.

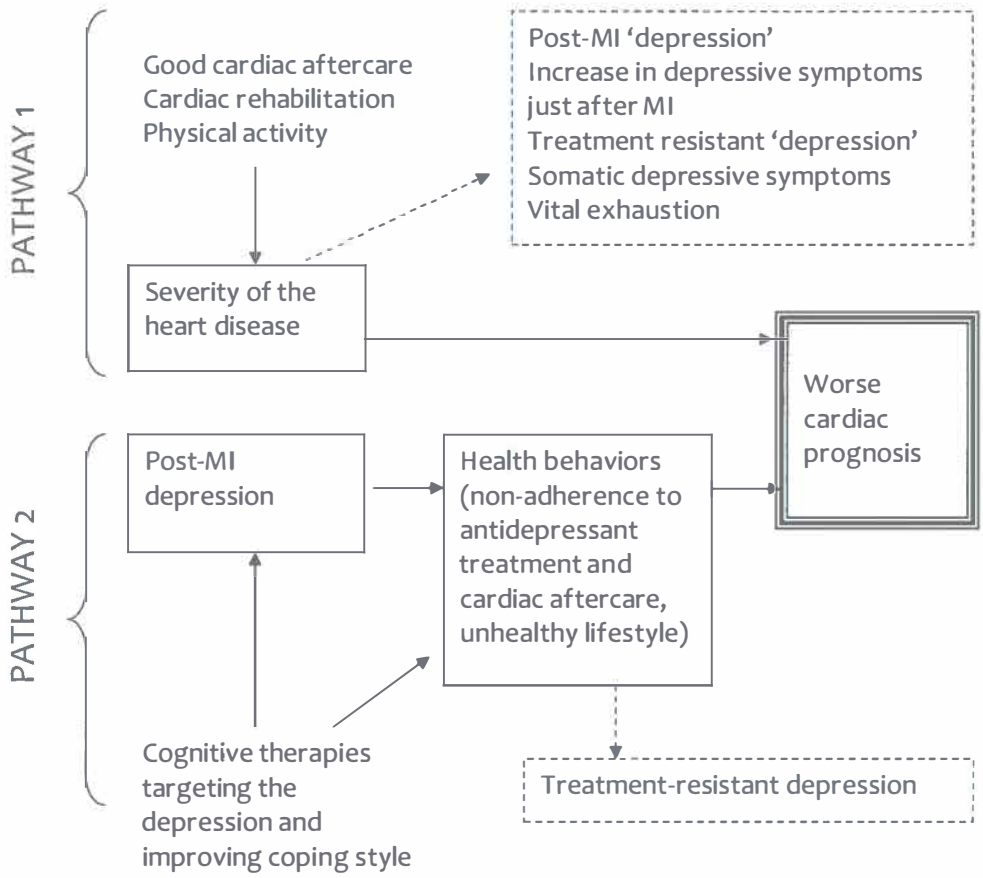

Figure 1. Schematic representation of association between post-MI depression and cardiac prognosis and potential treatments that could both improve depression and cardiac prognosis

This model is consistent with a recently published model integrating the literature of post-MI depression (264). According to this model, there are two pathways to post-MI depression. In the first, post-MI depression is a reflection of underlying biological processes including the underlying heart disease, inflammation, dysfunction of the hypothalamic pituitary-adrenal axis and the autonomic nervous system. This type of depression is dominated by somatic symptoms of depression, likely persists over time and is associated with worse cardiac prognosis. In the second pathway, post-MI depression is a result of vulnerability to stressful life events (i.e. the MI). This type of depression is dominated by cognitive symptoms of depression, usually improves over time and is less cardiotoxic than somatic depression. Both types of depression may be present in one patient and persistence of the depressive symptoms is cardiotoxic for both types of depression.

Both models stress the important role of the severity of the underlying heart disease and lifestyle behaviors in the association between post-MI depression and cardiac prognosis.

Directions for future research

Based on the findings from the present thesis and the literature, there appear to be two major pathways how depression after MI affects cardiac prognosis, which are represented in **Figure 1**.

Future trials are needed to evaluate the effectiveness of interventions targeting at these two pathways on depression outcomes and cardiac prognosis. According to **Figure 1**, interventions aimed to improve cardiac prognosis associated with post-MI depression should target the heart disease itself. Furthermore, it shows that interventions targeting at depression could only improve cardiac prognosis by improving treatment-nonadherence and lifestyle factors. Thus an intervention targeting at the heart disease itself should be supplemented by a depression treatment targeting at coping styles to improve the treatment-nonadherence.

An intervention that seems promising in improving both depression and the heart disease is physical exercise. Randomized trials in heart disease

patients have shown that cardiac rehabilitation with exercise therapy is associated with large reductions in subsequent cardiac events (23). Randomized trials in patients with major depression, but no heart disease, have shown that exercise therapy successfully improves depression (230, 231). Furthermore, completing cardiac rehabilitation programs with exercise therapy in heart disease patients has been found to reduce depressive symptoms as well as improving the heart disease, but this has only been found in non-randomized studies (164, 165, 259). Therefore, a randomized controlled trial is needed to evaluate the effects of exercise therapy on depression and cardiac prognosis in depressed MI patients.

Furthermore, future intervention trials aiming to improve cardiac prognosis should include patients with elevated somatic depressive symptoms, vital exhaustion and persisting depression rather than using major depression as an inclusion criterion. One trial used elevated symptoms of vital exhaustion as an inclusion criterion, but found the intervention not to be effective in improving cardiac prognosis. This may be explained by the intervention not targeting the factor underlying the symptoms of vital exhaustion, which is the heart disease itself (249).

Thus, a trial including MI patients with somatic depressive symptoms, vital exhaustion or persisting depression evaluating the effects of an intervention targeting the heart disease, such as exercise therapy, supplemented by an intervention improving non-adherence and lifestyle factors could be promising in improving cardiac prognosis.

Clinical implications

Chapter 2 showed that there is no evidence that structurally screening for depression in cardiologic care settings leads to improvements in depression or cardiac prognosis, mainly because treating major depression improved depression only modestly and did not improve cardiac prognosis. Perhaps structural screening for somatic depressive symptoms, or a repeated screen to identify persisting depression followed by treatments improving the heart disease supplemented by treatments targeting coping style to improve health behaviors will improve 'depression' as well as cardiac prognosis. The effects of this type of screening as well as the treatments on depression and cardiac prognosis still need to be investigated in randomized controlled trials.

In the meantime, treating specialists should be extra alert when a patient is showing somatic symptoms of depression or vital exhaustion, and when the depressive symptoms persist over time. This patient may have a deteriorating heart disease and/or may take less care of his/her health. First of all, the clinical course of the heart disease of such a patient must be monitored extra closely and they should be offered exercise therapy in addition to their cardiac rehabilitation program. Furthermore, serious attempts must be made to convince the patient of the importance of following and completing the cardiac rehabilitation program, as well as changing lifestyle factors and adhere to their cardiac medications. Especially patients who appear unwilling to follow the cardiac rehabilitation program and change their lifestyle must be persuaded to follow these programs and care better for their health. If necessary, the cardiac aftercare for these patients could be supplemented with a behavioral activation therapy.

Concluding remark

Taken together, depressed MI patients have consistently been found to have worse cardiac prognosis than non-depressed MI patients. Therefore, it was hoped that treatment of the depression would improve cardiac prognosis. It did not, and besides, it improved the depression itself only modestly. Perhaps better care for the heart can improve depression.

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English Summary

Within the first month after a heart attack (myocardial infarction (MI)), about 20% of the patients experience a major depressive episode. This is remarkably higher than in the general population, where the 12-month prevalence of major depression is approximately 5%. Compared to non-depressed MI patients, depressed MI patients have a reduced quality of life, greater functional impairments, an unhealthier lifestyle, are less adherent to lifestyle modification, cardiac aftercare, and cardiac rehabilitation, make higher health-care costs, and have a 2 to 2.5 times higher risk of getting a new cardiac event or death after the MI. For this reason, several clinical guidelines recommend that heart disease patients should be screened for depression structurally.

Chapter 2 presents a systematic review of the literature to evaluate what the empirical evidence is that screening heart disease patients for depression leads to improvements in depression and cardiac prognosis. It is concluded that there is no evidence yet that the benefits of screening outweigh the harms. The two main reasons for this conclusion are: 1) treatment for depression in heart disease patients improves depression only modestly and does not improve cardiac outcomes, and 2) no study evaluated the potential harms and benefits of screening for depression in heart disease patients.

Chapter 3 presents results from the Myocardial Infarction and Depression Intervention Trial (MIND-IT). This is a randomized controlled trial evaluating the effects of treatment for depression in depressed MI patients on the risk of new cardiac events or mortality during a mean follow-up of 5 years. Patients in the intervention group (n=209) were given feedback about their depression status and were offered several treatment options, including pharmacological and non-pharmacological treatment for depression, but they could also choose not to be treated for depression. Patients randomized to the care as usual group (n=122) were not given feedback about their depression status, but were told that they were free to seek treatment for mood problems outside the study, which was monitored. The intervention was not effective in reducing the risk of new cardiac events and mortality in both men and women. Interestingly, patients who actually received depression treatment, regardless of randomization status, had better survival rates than those who did not receive

depression treatment. It remains unclear whether this is due to the treatment itself or to a factor associated with both receiving treatment and survival, such as a healthier lifestyle of the patient.

In *Chapter 4* two hypotheses are formulated to explain why depression treatment in MI patients does not improve cardiac prognosis. The first states that depression treatment is only in some patients effective in reducing depression, and that particularly those MI patients in whom depression treatment is not effective in reducing depression, have the highest risk of new cardiac events and mortality. The second hypothesis states that it is not depression itself that predicts the worse cardiac prognosis. Namely, the association between depression and cardiac prognosis may be completely explained by factors that underlie both the depression and the worse prognosis, such as the severity of the heart disease itself. If depression treatments do not target these factors, they do not improve cardiac outcomes. Furthermore, worse prognosis may also be present in heart disease patients with elevated depressive symptoms, but not meeting diagnostic criteria for major depression. By using major depression as an inclusion criterion, the antidepressant treatment trials may have excluded a high-risk group of heart disease patients. In *Chapters 5 to 9* these two hypotheses are explored.

Chapter 5 explores the association between first-ever depression, treatment-resistant depression and cardiac prognosis. Several previous studies found first-ever depression to be: 1) more resistant to antidepressant treatment, and 2) associated with an increased risk of new cardiac events and mortality, than recurrent depression after MI. Other studies found treatment-resistant depression after MI to be associated with a higher risk of new cardiac events and mortality than treatment-responsive depression. In the studied sample all these associations were also present. Furthermore, the results showed that first-ever depression and treatment-resistant depression operated as two independent risk factors for worse cardiac prognosis. This means that the presence of one of these subtypes of depression, in the absence of the other, can be associated with worse cardiac prognosis.

Chapter 6 presents a systematic literature review evaluating whether first-ever depression and depression with an onset after the acute cardiac event are subtypes of depression that are particularly associated with worse cardiac prognosis. Some studies indeed found MI patients with first-ever depression and depression with an onset after the MI indeed to have worse cardiac prognosis than those with recurrent depression and depression with an onset before the MI. However, others could not find such an association, and one study even found somewhat increased mortality rates for patients with depression that had an onset before the cardiac event. Large methodological differences between the studies, for instance in the assessment of recurrence and onset of the depression, could explain their inconsistent results. Due to these inconsistent results, however, it can not be firmly concluded that first-ever depression and depression with an onset after the cardiac event are particularly associated with worse cardiac prognosis.

In *Chapter 7* it is evaluated whether an increase in the number of depressive symptoms just after the MI is associated with worse cardiac prognosis. This, to explain why some studies found depressive episodes with an onset after the MI to be associated with worse cardiac prognosis than depressive episodes with an onset before the MI. During the year after the MI, patients were administered the CIDI (Composite International Diagnostic Interview) to evaluate the presence of a depressive episode after the MI. During this interview the presence of ten depressive symptoms after the MI as well as during the four weeks before the MI was asked. The increase in depressive symptoms just after MI was calculated by subtracting the number of symptoms during the four weeks before the MI from the number of depressive symptoms after the MI. The study included 767 MI patients of whom 442 met criteria for a diagnosis of depression after the MI. A dose-response relationship between the increase in depressive symptoms after MI and risk of new cardiac events or mortality was found. Each additional symptom increase accounted for a 15% increased risk. Although an increase in depressive symptoms after the MI was associated with the severity of the heart disease at baseline, adjustment for heart disease severity did not affect the association between the increase in depressive symptoms and cardiac prognosis. In addition, the association was independent

from the number of depressive symptoms just before MI. This means that the association is similarly strong in the following three situations: 1) when it leads to a new diagnosis of depression after the MI, 2) when it does not lead to a full diagnosis of depression after the MI, and 3) when it occurs on top of a pre-existing depressive episode in patients who had already a full diagnosis of depression before the MI. Thus, not only patients with new onset depression have worse cardiac prognosis, also patients with only subthreshold depressive symptoms after the MI and patients with a depressive episode that has an onset before the MI may be at increased risk, as long as there is an increase in depressive symptoms after the MI. The increase in depressive symptoms may have an etiology that is related to the MI itself. Future studies should further investigate potential factors underlying the worse prognosis associated with an increase in depressive symptoms after MI.

In *Chapter 8*, the risk of new cardiac events and mortality was evaluated in association with self-reported depressive symptoms on the Beck Depression Inventory (BDI) and with a diagnosis of clinical depression during the first 3 months post-MI obtained with the CIDI in 2,493 MI patients. The background for this research question is that most studies evaluating the prognostic impact of depression after MI used questionnaires to assess depressive symptoms, whereas trials evaluating the effects of antidepressant treatment in depressed MI patients used the presence of a diagnosis of depression as an inclusion criterion. There are, however, substantial differences between assessing depressive symptoms with a questionnaire and assessing the presence of a diagnosis of depression with an interview. Because of these differences depressive symptoms on a questionnaire and a diagnosis of depression obtained with an interview may have a different etiology in heart disease patients. In this chapter it is found that depressive symptoms assessed with the BDI are a stronger predictor of new cardiac events and mortality than a diagnosis of clinical depression assessed with the CIDI. Moreover, the increased risk associated with BDI-scores was mainly due to the somatic/affective depressive symptoms. Severity of the heart disease at baseline explained a third to half of the association between depressive symptoms and cardiac prognosis. The substantial role that the severity of the heart disease appears to play in the

association may explain why traditional antidepressant treatments in MI patients do not improve cardiac prognosis. Moreover, the results in this chapter suggest that by including only MI patients with a diagnosis of depression, antidepressant treatment trials have excluded a high-risk group.

Chapter 9 explores more deeply the concept of somatic/affective depressive symptoms that appeared to play such a large role in the increased risk of new cardiac events and mortality. In this chapter it is explored whether the overlap between somatic/affective depressive symptoms and vital exhaustion is larger than the overlap between cognitive/affective depressive symptoms and vital exhaustion. Vital exhaustion is a concept consisting of fatigue, irritability and demoralization that is assessed with the Maastricht Questionnaire. Previous studies found vital exhaustion in heart disease patients to be associated with an increased risk of new cardiac events and mortality. Several studies evaluated whether depression and vital exhaustion represent the same underlying concept in heart disease patients, but these found inconsistent results. Therefore, in this chapter it is evaluated whether vital exhaustion only overlaps with *a part of* depression, namely the somatic/affective depressive symptoms. In this study, 528 MI patients filled out the BDI and the Maastricht Questionnaire during hospitalization for the MI, and 3, 6 and 12 months later. It was evaluated whether the overlap between vital exhaustion and somatic/affective depressive symptoms was larger than the overlap between vital exhaustion and cognitive/affective depressive symptoms. Vital exhaustion appeared to overlap much stronger with somatic/affective depressive symptoms in three ways: 1) the correlation between the scores, 2) the associated risk of new cardiac events and mortality, and 3) the course of the scores during the year following MI. These results suggest that vital exhaustion and somatic/affective depressive symptoms may reflect the same underlying concept in MI patients.

Chapter 10 integrates the results shown in *Chapters 5 to 9* to evaluate the hypotheses posed in *Chapter 4* to explain why treatment for depression in MI patients does not improve cardiac prognosis.

The first hypothesis stated that depression treatment is only in some patients effective in reducing depression, and that particularly those MI patients

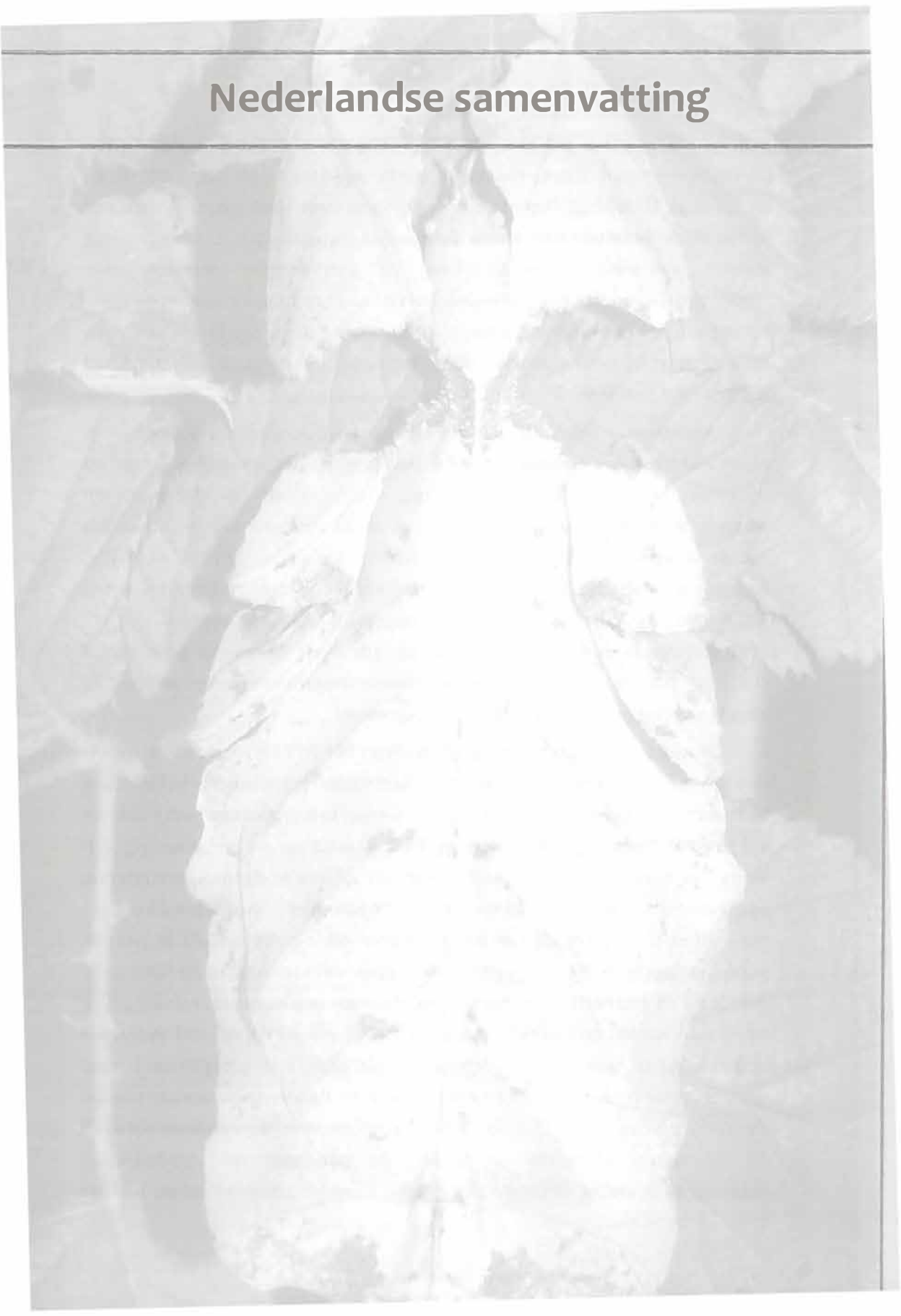
in whom depression treatment is not effective in reducing depression have the highest risk of new cardiac events and mortality. This hypothesis appears to be confirmed, since MI patients with treatment-resistant depression indeed had the highest risk of new cardiac events and mortality. There is no consistent evidence that such a subtype of depression mainly concerns first-ever depressive episodes or depressive episodes with an onset after the heart attack, as the results from some studies previously suggested. Two potential reasons for the worse prognosis associated with treatment-resistant depression are 1) treatment-non-adherence of the patient to both antidepressant treatment and cardiac aftercare regimens, 2) depression in these patients may be a reflection of a more severe and deteriorating underlying heart disease.

The second hypothesis stated that it is not depression itself that predicts the worse cardiac prognosis, but one or more factors associated with both depression and cardiac prognosis, such as the severity of the heart disease itself. A third to half of the association between depression and cardiac prognosis could be explained by measured parameters of the severity of the heart disease. The part that could not be explained may be explained by unmeasured or imprecisely measured parameters of heart disease severity or other factors. Thus, the association between depression and cardiac prognosis in MI patient may be less independent as is always suggested. If the association between depression and cardiac prognosis can completely be explained by underlying factors, such as the severity of the heart disease, then this could explain why antidepressant treatment (that does not change the underlying factors) does not improve cardiac prognosis. Moreover, the worse cardiac prognosis associated with post-MI depression appears to be due to somatic/affective depressive symptoms, an increase in depressive symptoms just after MI and in treatment-resistant depression, but not in a diagnosis of depression per se. By including only MI patients with a diagnosis of depression, antidepressant treatment trials may not have used optimal inclusion criteria.

Taken together, it appears that MI patients with the highest risk of getting new cardiac events are those who do not respond to antidepressant treatment, those with an increase in depressive symptoms just after MI, and those with somatic/affective depressive symptoms. Treatment-non-adherence and the severity of the heart disease itself may play a substantial role in the

increased risk in these patients. A trial including specifically these patients that evaluates a treatment targeting the factors underlying the increased risk, such as the severity of the heart disease and treatment-non-adherence, will be more promising in improving the cardiac prognosis than the traditional antidepressant treatments.

Nederlandse samenvatting



In de eerste maand na een hartinfarct heeft ongeveer 20% van de patiënten een depressieve episode. Deze prevalentie is ongeveer 4 tot 5 keer hoger dan die bij de gewone bevolking. Depressie na een hartinfarct gaat gepaard met een verminderde kwaliteit van leven, functionele beperkingen, een ongezonde leefstijl, verminderde therapietrouw en verminderde deelname aan hartrevalidatie, hogere gezondheidskosten en een 2 tot 2,5 keer verhoogd risico op het krijgen van nieuwe hartproblemen of vervroegd overlijden. Om deze redenen staat in verscheidene richtlijnen het advies om hartpatiënten standaard op depressie te testen.

Hoofdstuk 2 beschrijft een literatuuronderzoek waarin systematisch is onderzocht wat het wetenschappelijke bewijs is dat het structureel testen op depressie bij hartpatiënten leidt tot verbeteringen in depressie en hartprognose. Geconcludeerd wordt dat er op dit moment nog geen bewijs is dat de voordelen ervan tegen de eventuele risico's opwegen. De verklaring hiervoor is tweeledig. Ten eerste leidt depressiebehandeling bij hartpatiënten tot slechts minimale verbeteringen in depressie en zelfs helemaal niet tot verbeteringen in de hartprognose. Ten tweede heeft tot nu toe geen enkele studie onderzocht wat de mogelijke positieve en negatieve effecten zijn van het structureel testen van hartpatiënten op depressie.

Hoofdstuk 3 beschrijft de resultaten van MIND-IT (Myocardial INfarction and Depression Intervention Trial). Dit is een studie naar depressiebehandeling bij hartinfarctpatiënten op het krijgen van nieuwe hartproblemen gedurende de vijf jaren na de depressiebehandeling. De 209 patiënten in de behandelgroep kregen te horen dat zij depressief waren en ze kregen daarop verschillende depressiebehandelingen aangeboden, waaronder antidepressiva of psychotherapie. Echter, zij konden ook kiezen om niet behandeld te worden voor hun depressie. De 122 patiënten in de controlegroep kregen de nazorg die standaard na een hartinfarct gegeven wordt, maar hen werd niet verteld dat zij depressief waren. Wel werd hen verteld dat zij vrij waren om zelf eventueel behandeling te zoeken tegen depressieve klachten, wat geregistreerd werd door de onderzoekers. Er waren geen verschillen tussen de behandelgroep en de controlegroep in het risico op nieuwe hartproblemen gedurende de vijf jaren na de depressiebehandeling. Echter, de patiënten die daadwerkelijk depressiebehandeling ontvingen, ongeacht in welke groep zij zaten, hadden

een lager risico op overlijden dan diegenen die geen depressiebehandeling ontvingen. Dit kan liggen aan de depressiebehandeling zelf, maar kan ook komen doordat mensen die kiezen voor zo'n behandeling een grotere overlevingskans hebben vanwege factoren als een gezondere leefstijl en therapietrouw.

In *Hoofdstuk 4* worden twee mogelijke verklaringen geïntroduceerd waarom depressiebehandeling bij hartinfarctpatiënten de hartprognose niet verbetert. De eerste verklaring luidt dat depressiebehandeling alleen bij sommige hartinfarctpatiënten effectief is in het verbeteren van de depressie, en dat juist de hartinfarctpatiënten waarin de behandeling niet effectief is het hoogste risico op nieuwe hartproblemen hebben. De tweede verklaring luidt dat het niet echt depressie is die de slechte hartprognose veroorzaakt, maar eerder een factor die zowel met depressie als met de slechte hartprognose geassocieerd is, zoals een ernstigere conditie van het hart. Een depressiebehandeling die niet dit soort factoren beïnvloedt, zal de hartprognose niet verbeteren. Bovendien zouden depressieve klachten, zonder te voldoen aan de diagnose van depressie, al voldoende zijn om een verhoogd risico op nieuwe hartproblemen te hebben. Studies naar de effecten van depressiebehandeling bij hartinfarctpatiënten zijn tot nu toe alleen uitgevoerd bij hartinfarctpatiënten die voldoen aan de diagnose depressie. Dit zou betekenen dat deze studies misschien wel een hoogrisico groep hebben uitgesloten van deelname, namelijk diegenen met depressieve klachten die niet voldoen aan de diagnose depressie. In *Hoofdstukken 5* tot en met 9 worden deze twee mogelijke verklaringen onderzocht.

In *Hoofdstuk 5* wordt onderzocht hoe het hebben van een eerste episode van depressie, het wel of niet reageren op depressiebehandeling en het risico op nieuwe hartproblemen met elkaar samenhangen. Eerdere studies onder hartinfarctpatiënten vonden namelijk dat diegenen die voor het eerst depressief waren slechter reageren op depressiebehandeling en tevens een hoger risico hadden op het krijgen van nieuwe hartproblemen dan diegenen met recidiverende episoden van depressie. Uit andere studies bleek dat depressieve hartpatiënten waarbij de depressie niet reageerde op depressiebehandeling een hoger risico op nieuwe hartproblemen hebben dan diegenen waarbij de depressie wel op depressiebehandeling reageerde. In de huidige steekproef

bleken al deze verbanden ook te bestaan. Daarbij werd gevonden dat het hebben van een eerste depressieve episode (in plaats van recidiverend) en het hebben van een depressie die niet op depressiebehandeling reageerde (in plaats van wél) beide onafhankelijk van elkaar het risico op nieuwe hartproblemen verhoogden. Dit houdt in dat de aanwezigheid van één van deze beide al tot een verhoogd risico op nieuwe hartproblemen kan leiden.

Hoofdstuk 6 beschrijft de resultaten van een literatuuronderzoek. Hierin is systematisch onderzocht of een eerste depressieve episode en een depressieve episode die pas na het hartinfarct ontstaan is een hoger risico op het krijgen van nieuwe hartproblemen met zich meebrengt dan een recidiverende episode of een depressieve episode die al vóór het hartinfarct ontstaan is. Sommige studies vonden inderdaad een verhoogd risico op nieuwe hartproblemen bij hartinfarctpatiënten met eerste depressieve episoden en episoden die pas na het hartinfarct ontstaan zijn. Echter, andere studies vonden geen verschillen in het risico op nieuwe hartproblemen bij hartpatiënten met eerste en recidiverende depressieve episoden en bij hartpatiënten met depressieve episoden die voor of na het hartinfarct ontstaan zijn. Eén studie vond zelfs een hoger risico op nieuwe hartproblemen bij patiënten met een depressieve episode die vóór het hartinfarct ontstaan is. De resultaten van de studies zijn dus erg wisselend. Substantiële methodologische verschillen tussen de onderzochte studies, bijvoorbeeld in het meten van recidiveren en het moment van ontstaan van de depressie, verklaren mogelijk deze wisselende resultaten. Door deze wisselende resultaten kan op dit moment niet geconcludeerd worden of hartinfarctpatiënten met een eerste depressie of een depressie die pas na het hartinfarct ontstaan is een hoger risico op nieuwe hartproblemen hebben dan diegenen met recidiverende depressie of depressie die al vóór het hartinfarct ontstaan is.

In *Hoofdstuk 7* is onderzocht of een grotere toename van het aantal depressieve symptomen vlak na het hartinfarct is geassocieerd met een groter risico op het krijgen van nieuwe hartproblemen. Dit, om te kunnen verklaren waarom sommige studies vonden dat nieuw ontstane depressie na het hartinfarct geassocieerd is met een verhoogd risico op nieuwe hartproblemen. Gedurende het jaar na het hartinfarct werd bij de patiënten de CIDI (Composite International Diagnostic Interview) afgenomen om de aanwezigheid van de

diagnose depressie vast te stellen. Tijdens dit interview werd de aanwezigheid van 10 depressieve symptomen zowel na het hartinfarct als gedurende de vier weken voor het hartinfarct uitgevraagd. De toename van het aantal depressieve symptomen na het hartinfarct werd berekend door het aantal symptomen gedurende de vier weken voor het hartinfarct af te trekken van het aantal dat aanwezig was na het hartinfarct. De studie omvatte 767 hartinfarctpatiënten, waarvan 442 na het hartinfarct aan de diagnose depressie voldeden. Er was een dosis-effect relatie tussen de toename van aantal depressieve symptomen na het hartinfarct en het krijgen van nieuwe hartproblemen. Ieder symptoom dat erbij kwam was geassocieerd met een toename van 15% in het risico op nieuwe hartproblemen. Een grotere toename van het aantal depressieve symptomen was geassocieerd met een ernstiger onderliggende hartziekte. Echter, het controleren voor de ernst van de hartziekte verzwakte niet het verband tussen de toename van depressieve symptomen en het risico op nieuwe hartproblemen. Daarnaast bleek dat het verband onafhankelijk was van het aantal depressieve symptomen gedurende de 4 weken vóór het hartinfarct. Dit betekent dat een toename van bijvoorbeeld twee symptomen even sterk geassocieerd was met het krijgen van nieuwe hartproblemen in de volgende drie situaties: 1) wanneer de toename niet leidde tot de diagnose van depressie na het hartinfarct, 2) wanneer de toename leidde tot een nieuw ontstane diagnose van depressie na het hartinfarct, en 3) wanneer de toename plaatsvond bovenop de al bestaande diagnose van depressie. Dus niet alleen hartinfarctpatiënten met nieuw ontstane depressie na het hartinfarct hebben een verhoogd risico op het krijgen van nieuwe hartproblemen, maar ook diegenen zonder de diagnose depressie na het hartinfarct en diegenen met een depressie die al voor het hartinfarct aanwezig was, kunnen een verhoogd risico op nieuwe hartproblemen hebben, zolang er maar een toename is van het aantal depressieve symptomen na het hartinfarct. Mogelijk ligt een ernstiger hartinfarct ten grondslag aan een grotere toename van het aantal depressiesymptomen. Het moet nog onderzocht worden welke factoren het verhoogde risico op nieuwe hartproblemen geassocieerd met een toename van depressieve symptomen kunnen verklaren.

In *Hoofdstuk* 8 wordt het risico op het krijgen van nieuwe hartproblemen geassocieerd met enerzijds door de patiënt gerapporteerde depressieve

symptomen op een depressievragenlijst (de BDI; Beck Depression Inventory) en anderzijds een diagnose van depressie bepaald met behulp van een diagnostisch interview (de CIDI). De gedachte hierachter is dat in de meeste studies die onderzochten wat het effect van depressie na een hartinfarct is op het krijgen van nieuwe hartproblemen een vragenlijst is gebruikt om depressie te meten, terwijl de studies naar depressiebehandeling juist alleen werden uitgevoerd onder hartinfarctpatiënten die voldeden aan de diagnose van depressie bepaald met behulp van een interview. Er zijn echter substantiële verschillen tussen het meten van depressieve symptomen op een vragenlijst en het meten van de diagnose van depressie middels een interview. Door deze verschillen kan het zijn dat bij hartpatiënten verschillende factoren ten grondslag liggen aan de aanwezigheid van depressieve symptomen op een vragenlijst en de aanwezigheid van de diagnose van depressie gemeten met een interview. In dit hoofdstuk wordt bij 2,493 hartinfarctpatiënten gevonden dat depressieve symptomen op de BDI een sterkere voorspeller zijn voor het krijgen van nieuwe hartproblemen dan een diagnose van depressie. Depressieve symptomen op de BDI voorspellen het krijgen van nieuwe hartproblemen zowel in de aan- als in de afwezigheid van een diagnose van depressie. Bovendien blijkt het risico vooral te zitten in een bepaald symptoomprofiel, namelijk de somatisch/affectieve symptomen. Een derde tot de helft van het verband tussen BDI-scores en nieuwe hartproblemen wordt verklaard door de ernst van de hartziekte. Het feit dat de ernst van de hartziekte zelf zo'n grote rol speelt in het verband tussen depressie en het krijgen van nieuwe hartproblemen, kan mogelijk verklaren waarom studies naar depressiebehandeling bij hartpatiënten de hartprognose niet verbeteren. Bovendien suggereren de resultaten van deze studie dat de studies naar depressiebehandeling die alleen werden uitgevoerd onder hartpatiënten met de diagnose van depressie misschien niet de juiste inclusiecriteria hebben gebruikt.

In *Hoofdstuk 9* wordt verder ingegaan op de somatisch/affectieve depressieve symptomen van de BDI, die in het vorige hoofdstuk zo'n groot aandeel leverden aan het risico op nieuwe hartproblemen. In dit hoofdstuk wordt onderzocht of de overlap tussen somatisch/affectieve depressieve symptomen en vitale uitputting groter is dan die tussen cognitief/affectieve depressieve symptomen en vitale uitputting. Vitale uitputting is een concept

bestaande uit vermoeidheid, agitatie en moedeloosheid dat gemeten kan worden met een vragenlijst, de MQ (Maastricht Questionnaire). Voorgaande studies vonden dat vitale uitputting bij hartpatiënten geassocieerd is met een verhoogd risico op nieuwe hartproblemen. Een aantal studies hebben onderzocht of vitale uitputting en depressie bij hartpatiënten niet hetzelfde concept representeren, maar die vonden tegenstrijdige resultaten. In dit hoofdstuk wordt daarom onderzocht of vitale uitputting alleen overlapt met *een deel van* depressie, en wel dat deel van depressie, dat geassocieerd is met het hoogste risico op nieuwe hartproblemen: somatisch/affectieve depressieve symptomen. Hiertoe hebben 528 hartinfarctpatiënten in het ziekenhuis en op 3, 6 en 12 maanden na het infarct zowel de BDI als de MQ ingevuld. Onderzocht werd of de overlap tussen vitale uitputting en somatisch/affectieve depressieve symptomen groter was dan die tussen vitale uitputting en cognitief/affectieve depressieve symptomen. Vitale uitputting bleek veel sterker te overlappen met somatisch/affectieve depressieve symptomen dan met cognitief/affectieve depressieve symptomen op drie vlakken, namelijk: 1) de correlatie tussen de scores, 2) de associatie met het krijgen van nieuwe hartproblemen en 3) het beloop van de scores gedurende het jaar na het hartinfarct. Mogelijk weerspiegelen vitale uitputting en somatisch/affectieve depressieve symptomen bij hartinfarctpatiënten hetzelfde onderliggende concept.

Hoofdstuk 10 integreert de bevindingen van *Hoofdstukken 5* tot *en met 9*. Met behulp van die bevindingen wordt geprobeerd om de twee verklaringen genoemd in *Hoofdstuk 4*, waarom depressiebehandeling in hartinfarctpatiënten niet tot verbeteringen in hartprognose leidt, te evalueren. De eerste verklaring luidde dat depressiebehandeling alleen bij sommige hartinfarctpatiënten effectief is in het verbeteren van de depressie, en dat juist de hartinfarctpatiënten waarbij de behandeling niet effectief is het hoogste risico op nieuwe hartproblemen hebben. Dit lijkt inderdaad bevestigd, aangezien hartinfarctpatiënten met een depressie die niet reageerde op depressiebehandeling, het hoogste risico op nieuwe hartproblemen hebben. Dit zijn overigens niet alleen maar diegenen met een eerste depressieve episode of een episode die pas na het hartinfarct ontstaan is, zoals de resultaten van sommige voorgaande studies deden vermoeden. Twee mogelijke redenen waarom diegenen waarin depressiebehandeling niet effectief is een verhoogd

risico op nieuwe hartproblemen hebben, zijn: 1) therapieontrouw van de patiënt aan zowel de depressiebehandeling als de hartgerelateerde nazorg, 2) de depressie bij deze patiënten is een weerspiegeling van een ernstige onderliggende hartziekte die verslechtert over de tijd. De tweede verklaring genoemd in *Hoofdstuk 4* luidde dat het niet echt depressie is die de nieuwe hartproblemen veroorzaakt, maar eerder een factor die zowel met depressie als met de nieuwe hartproblemen geassocieerd is, zoals een ernstigere conditie van het hart. Gevonden werd dat tot de helft van het verband tussen depressieve symptomen en nieuwe hartproblemen verklaard wordt door de conditie van het hart. De andere helft van het verband die niet verklaard kon worden zou heel goed nog door niet of slecht gemeten parameters verklaard kunnen worden. Het verband tussen depressie en hartprognose lijkt dus minder onafhankelijk te zijn dan vaak gesuggereerd wordt. Als het verband tussen depressie en hartprognose voor een groot deel of volledig verstoord wordt door zulke onderliggende factoren, kan dit verklaren waarom depressiebehandeling (die niet gericht is op het veranderen van die onderliggende factoren) de hartprognose niet verbetert. Bovendien lijkt het verhoogde risico op nieuwe hartproblemen vooral te liggen in een toename in depressieve symptomen na het hartinfarct, in somatisch/affectieve depressieve symptomen en vitale uitputting, maar niet zozeer in een diagnose van depressie. Hierdoor hebben de studies naar depressiebehandeling, die alleen werden uitgevoerd onder hartpatiënten met de diagnose depressie, een groep hartpatiënten met verhoogd risico op nieuwe hartproblemen uitgesloten. Samengevat lijkt het erop dat die hartinfarctpatiënten met het hoogste risico op nieuwe hartproblemen diegenen zijn met depressie die niet reageert op depressiebehandeling, diegenen met een toename in depressieve symptomen na het hartinfarct, en diegenen met somatisch/affectieve depressieve symptomen of vitale uitputting. Therapieontrouw en de ernst van de hartziekte zelf zijn twee belangrijke potentiële verklaringen voor het verhoogde risico bij deze patiënten. Een studie specifiek uitgevoerd onder deze hoogrisico groepen die een behandeling toetst die gericht is op de factoren die ten grondslag liggen aan dit verhoogde risico, de ernst van de hartziekte en therapieontrouw, heeft mogelijk meer kans van slagen in het verbeteren van de hartprognose dan de traditionele depressiebehandelingen.

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Curriculum Vitae

Marij Zuidersma was born on 14th of September 1979 in Groningen. In 1998, she started her study biology at the Rijksuniversiteit Groningen. Her first research internship took place at the Biology Department of the University of Groningen. The subject was about the effects of light on sleepiness and waking EEG in humans, supervised by Domien Beersma and Marijke Gordijn. Her second research internship took place at the Ludwig Bolzmann Institute for Urban Ethology, University of Vienna. The subject was about male partner choice according to female body odour, depending on phase of the menstrual cycle and female personality, supervised by Karl Grammer. Marij obtained her Master's degree in 2003. In 2008 she started her PhD project at the Interdisciplinary Center for Psychiatric Epidemiology and graduate school SHARE, which resulted in this thesis. Currently, she is working as a post-doc at the Department of Epidemiology at the University Medical Centre Groningen.

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